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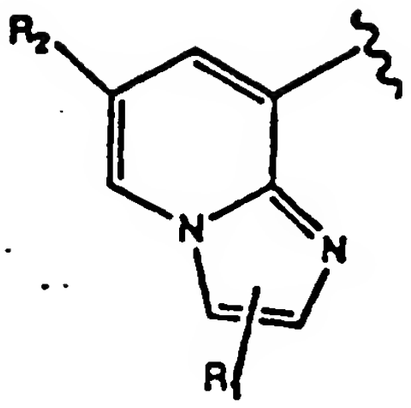
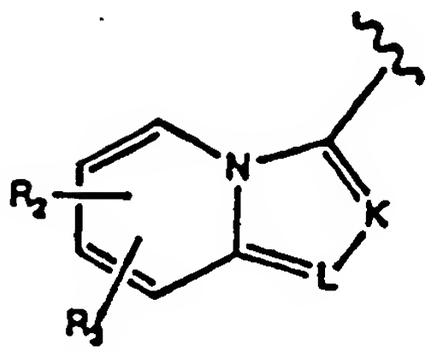
(54) New imidazopyridines as serotonergic 5-HT3 antagonists.

(57) The imidazopyridines of formula
wherein Ar represents a radical of the formula

EP 0 504 679 A1



A



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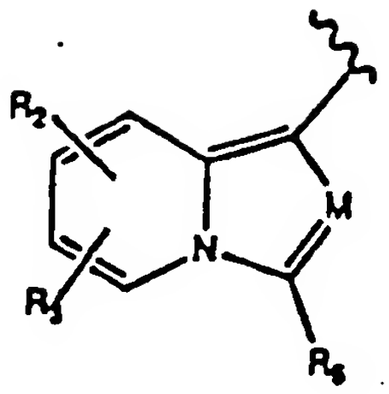

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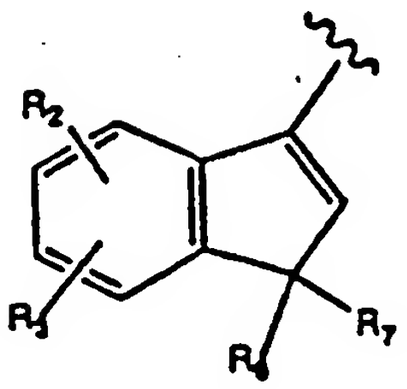

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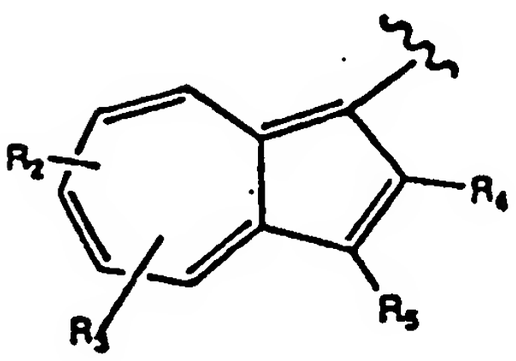

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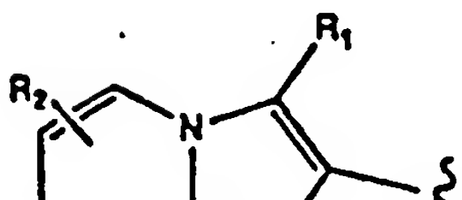

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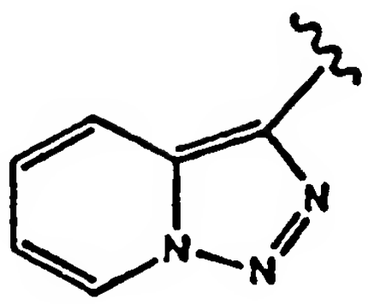

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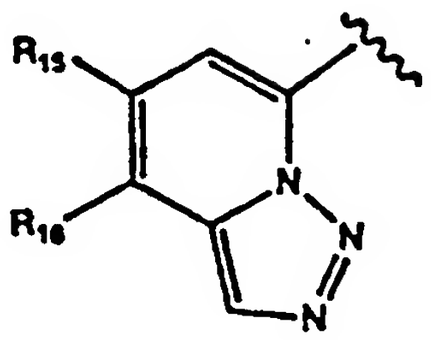
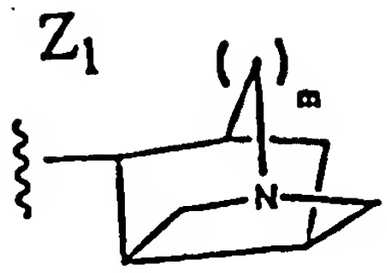


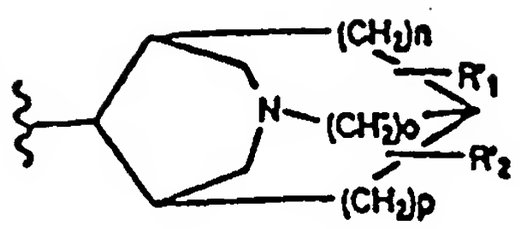
H

Z represents a radical of the formula

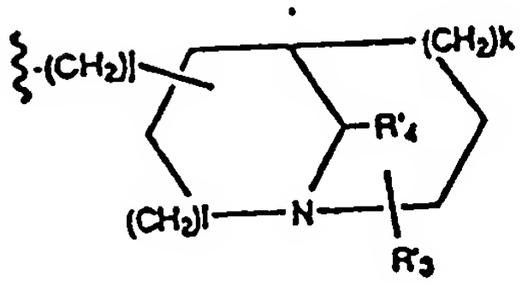
Z_1



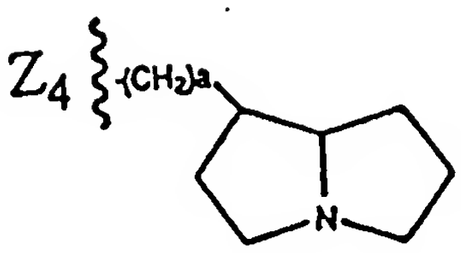
Z_2



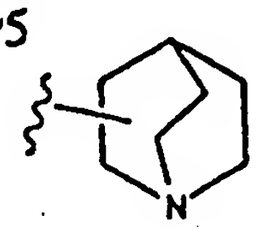
Z_3



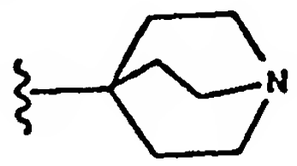
Z_4



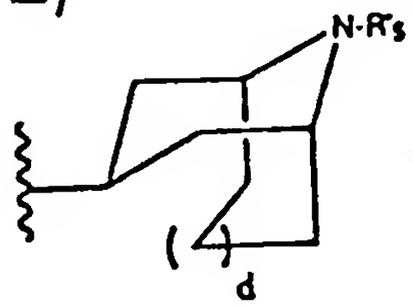
Z_5



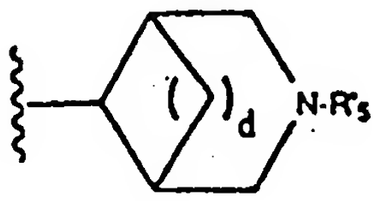
Z_6



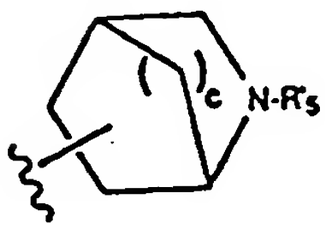
Z_7



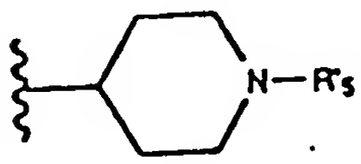
Z_8



Z_9



Z_{10}



Z_{11}

Z_{12}

The compounds are seterotonergic 5-HT_3 antagonists. As such they are useful for the treatment of humans and animals wherein antagonism of 5-HT_3 receptors is beneficial. Therapy is indicated for, but not limited to, the treatment of anxiety, psychoses, depression (especially depression accompanied by anxiety), cognitive disorders, substance abuse dependence and withdrawal, gastrointestinal motility disturbancies (including esophageal reflux, dyspepsia, gastric stasis, irritable bowel syndrome), emesis caused by chemotherapeutic agents, and visceral pain. Additionally, the compounds of the present invention may find utillity as enhancers of nasal absoption of bioactive compounds.

BACKGROUND OF THE INVENTION

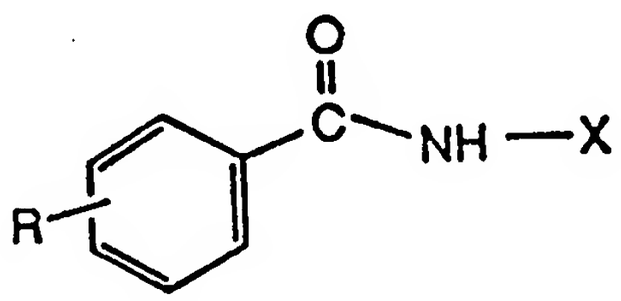
The invention herein is directed to compounds and a method of treating gastrointestinal motility disorders of a mammal by administering to the mammal in need thereof a therapeutically effective amount of a compound disclosed herein or a pharmaceutically acceptable salt thereof. The method can be practiced to treat gastrointestinal motility disorders such as gastroesophageal reflux, diseases characterized by delayed gastric emptying, ileus, irritable bowel syndrome, and the like. The compounds of the invention are serotonergic 5-HT_3 antagonists and as such are useful for the treatment of conditions, for example, such as anxiety, psychoses and depression.

There are classes of compounds known for the treatment of such disorders. For example, azatetracycle compounds are disclosed in co-pending U.S. patent application serial no. 07/515,391 filed April 27, 1990, and N-Azabicyclo [3.3.0] octane amides of aromatic acids are disclosed in co-pending application serial no. 07/406,205 filed September 11, 1989.

Aza-adamantyl compounds are disclosed in U.S. Patent 4,816,453 and are mentioned generically in U.K. Patent 2,152,049A and European application 0189002A2.

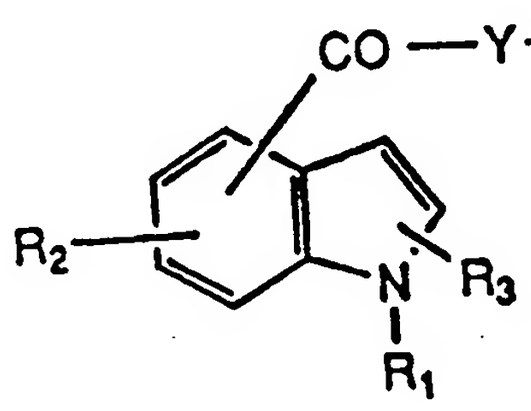
Azabicyclic nonanes are disclosed in European Patent application 0094742A2. Additional azabicyclic compounds are disclosed in U.S. Patents 4,797,387 and 4,797,406.

Benzamides have been known as 5-HT_3 antagonists and as compounds possessing gastrointestinal motility-enhancing properties. Benzamides of the following formula:



compounds wherein X can be an azabicycloalkane moiety and which exhibit gastrointestinal motility enhancing and/or 5-HT_3 antagonist properties are disclosed in EP 0094742A2 and in U.S. patent 4,797,406. In addition, UK Patent 2,152,049 discloses that certain benzamide derivatives exhibit serotonin M antagonistic activity.

Indoleamides of the following formula have also been described as possessing gastrointestinal motility-enhancing and/or 5-HT_3 antagonist properties:



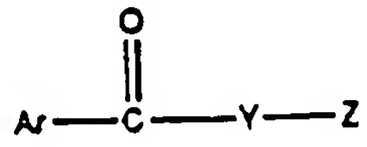
Compounds wherein X contains an aminergic side chain or an azabicycloalkane moiety are described in U.S. Patent 4,797,406.

European patent publication number 0,230,718 discloses certain substituted benzamide derivatives, substituted with piperidinyl analogues as having gastrointestinal motility-enhancing and/or antiemetic activity and/or 5-HT_3 receptor antagonist activity.

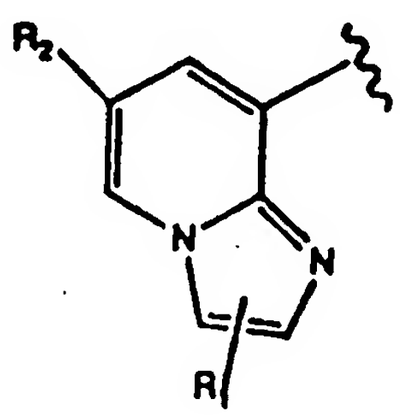
SUMMARY OF THE INVENTION

The compounds of the present invention are serotonergic 5-HT_3 antagonists. As such they are useful for the treatment of humans and animals wherein antagonism of 5-HT_3 receptors is beneficial. Therapy is indicated for, but not limited to, the treatment of anxiety, psychoses, depression (especially depression accompanied by anxiety), cognitive disorders, substance abuse dependence and withdrawal, gastrointestinal motility disturbancies (including esophageal reflux, dyspepsia, gastric stasis, irritable bowel syndrome),

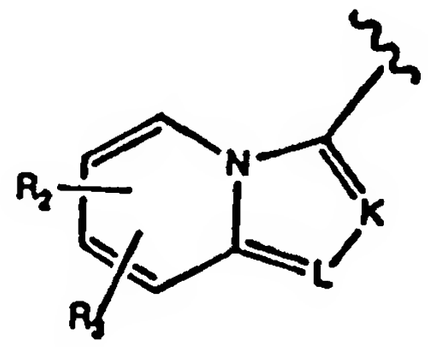
emesis caused by chemotherapeutic agents, and visceral pain. Additionally, the compounds of the present invention may find utility as enhancers of nasal absorption of bioactive compounds.
The invention herein is directed to compounds of the formula



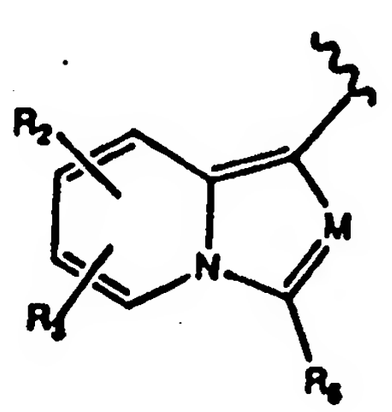
the stereoisomers and pharmaceutically acceptable salts thereof, wherein Ar represents a radical of the formula



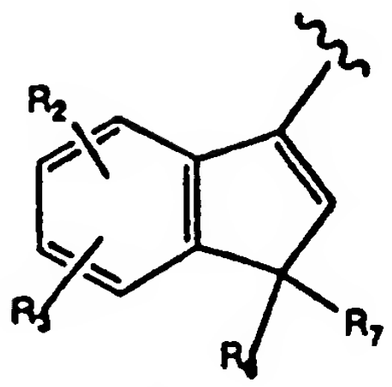
A



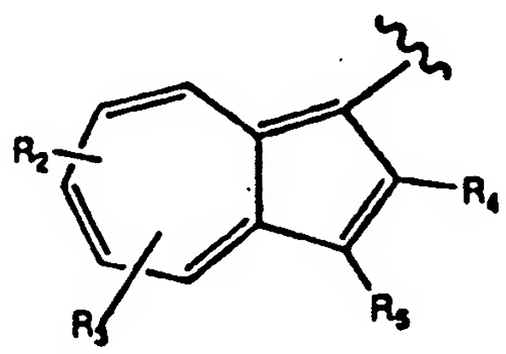
B



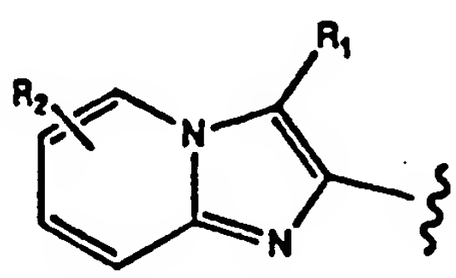
C



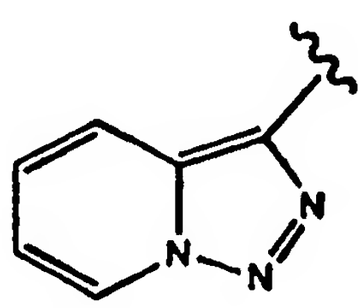
D



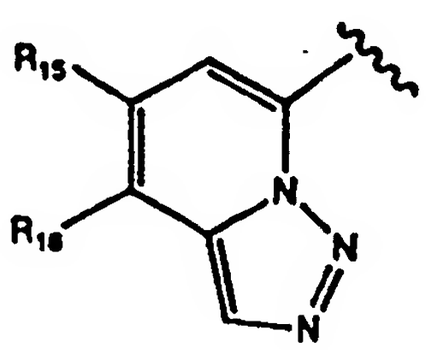
E



F



G



H

Wherein in group A R_1 is H, or C_{1-6} alkyl, and R_2 is H, or halogen;
In group B, K is N or CR_4, L is N or CR_5, R_2 & R_3 are independently H or halogen, R_4 is H, or C_{1-6} alkoxy and R_5 is H, halogen, CF_3, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkythio, C_{1-6} alkylsulfonyl, C_{1-6} alkylsulfinyl, C_{1-7} acyl, cyano, C_{1-6} alkoxycarbonyl, C_{1-7} acylamino, hydroxy, nitro, amino, aminocarbonyl, or aminosulfonyl optionally N-substituted by one or two groups selected from C_{1-6} alkyl, C_{3-8} cycloalkyl, and C_{3-8} cycloalkylC_{1-4}alkyl or disubstituted by C_4 or C_5 polymethylene; phenyl or phenyl C_{1-4} alkyl group optionally substituted in the phenyl ring by one or two of halogen, C_{1-6} alkoxy or C_{1-6} alkyl groups;
In group C, M is N or CR_4, R_2 & R_3 are independently H or halogen, R_4 is H or C_{1-6} alkoxy and R_5 is H, halogen, CF_3, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkylsulfonyl, C_{1-6} alkylsulfinyl, C_{1-7} acyl, cyano, C_{1-6} alkoxycarbonyl, C_{1-7} acylamino, hydroxy, nitro, amino, aminocarbonyl, or aminosulfonyl optionally N-substituted by one or two groups selected from C_{1-6} alkyl, C_{3-8} cycloalkyl, and C_{3-8} cycloalkylC_{1-4}alkyl or disubstituted by C_4 or C_5 polymethylene, phenyl or phenyl C_{1-4} alkyl group optionally the phenyl ring by one or two of halogen, C_{1-6} alkoxy or C_{1-6} alkyl groups;
In group D one of R_6 and R_7 is C_{1-6} alkyl and the other is C_{1-6} alkyl, phenyl or phenyl C_{1-4} alkyl

optionally substituted in either phenyl ring by one or two of C_{1-6} alkyl, C_{1-6} alkoxy, or halogen, or R_6 & R_7 together are C_{2-6} polymethylene or C_{2-5} polymethylene interrupted by an -O-linkage, and R_2 & R_3 are independently H or halogen;

In group E, R_4 is H or C_{1-6} alkoxy, R_5 is H or C_{1-6} alkoxy, and R_2 is H, halogen, CF_3, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkylsulfonyl, C_{1-6} alkylsulfinyl, C_{1-7} acyl, cyano, C_{1-6} alkoxycarbonyl, C_{1-7} acylamino, hydroxy, nitro, amino, aminocarbonyl, or aminosulfonyl, optionally N-substituted by one or two groups selected from C_{1-6} alkyl, C_{3-8} cycloalkyl, and C_{3-8} cycloalkylC_{1-4}alkyl or disubstituted by C_4 or C_5 polymethylene, phenyl or phenyl C_{1-4} alkyl group optionally substituted in the phenyl ring by one or two of halogen, C_{1-6} alkoxy or C_{1-6} alkyl groups, and R_2 & R_3 are independently H or halogen;

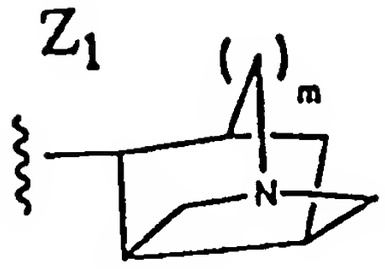
In group F, R_1 is H or C_{1-6} alkyl, and R_2 is H or halogen; and

in group H R_{15} & R_{16} are independently H or -CH = CH-CH = CH-;

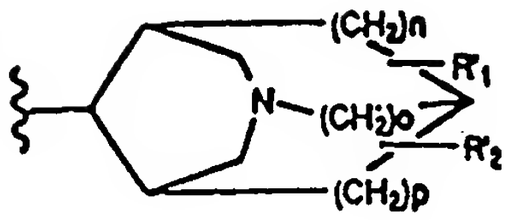
Y represents NH or O; and

Z represents a radical of the formula

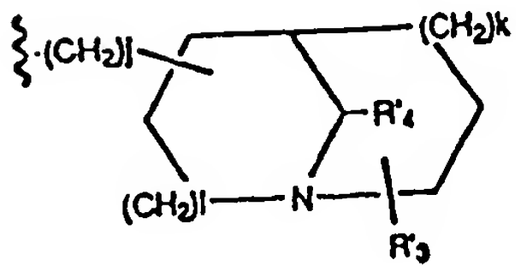
Z_1



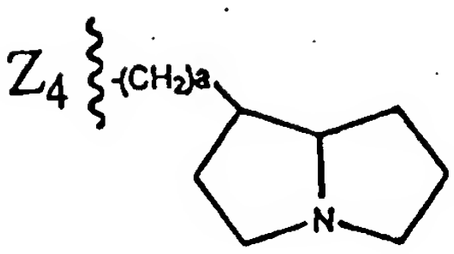
Z_2



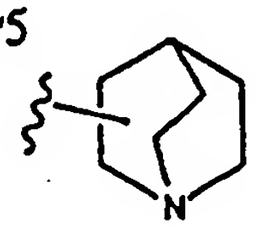
Z_3



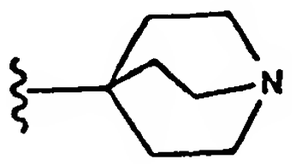
Z_4



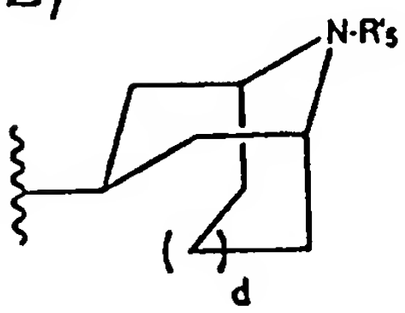
Z_5



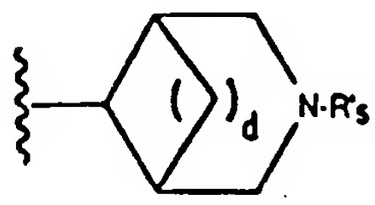
Z_6



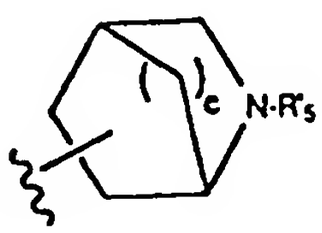
Z_7



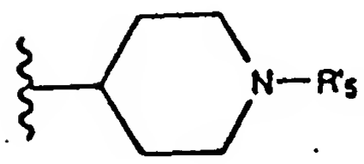
Z_8



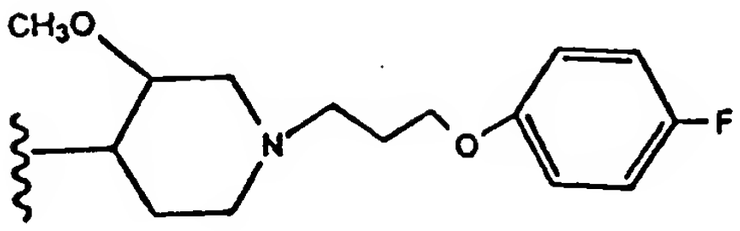
Z_9



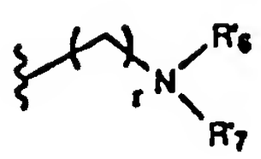
Z_{10}



Z_{11}



Z_{12}



Wherein in group Z_1 m is 1 or 2;

In group Z_2 n and p are independently 1 or 2 and o is 0, 1, or

2 such that n + p + o ≥ 3, and R'_1 and R'_2 are independently H, C_{1-6} alkyl, phenyl or phenyl-C_{1-6} alkyl, which phenyl moieties may be substituted by C_{1-6} alkyl, C_{1-6} alkoxy, or halogen;

In group Z_3 k is 0 to 2, 1 is 0 to 3, j is 0 to 4, and one of R'_3 and R'_4 is H, C_{1-6} alkyl, phenyl, or phenyl-C_{1-3} alkyl, which phenyl moieties may be optionally substituted by C_{1-6} alkyl, C_{1-6} alkoxy, CF_3 or halogen, and the other of R'_3 and R'_4 is H or C_{1-6} alkyl;

In group Z_4 a is 0 or 1;

In group Z_7 d is 0 or 1, and R'_5 is C_{1-7} alkyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkyl-C_{1-2} alkyl, C_{2-7} alkenyl, C_{2-7} alkylenyl-C_{1-4} alkyl, or phenyl-C_{1-6} alkyl.

In group Z_8 d and R'_5 are as previously defined;

In group Z_9 e is 1 or 2, and R'_5 is as previously defined;

In group Z_{10} R'_5 is as previously defined; and

In group Z_{12} r is 1 to 4, R'_6 and R'_7 are independently C_{1-6} alkyl, C_{1-6} alkenyl, or C_{1-6} alkynyl or together form -(CH2)s-, wherein s is 3-7 and one of the CH_2 units may optionally be replaced by -0-, or NR'_8, wherein R'_8 is H or C_{1-6} alkyl;

with the proviso that when Ar is group B, C, D or E, then Z cannot be Z_5, Z_7 or Z_9.

The term "cycloalkyl" embraces cyclic radicals having three to about ten ring carbon atoms, preferably three to about six carbon atoms, such as cyclopropyl and cyclobutyl. The term "haloalkyl" embraces radicals wherein any one or more of the alkyl carbon atoms is substituted with one or more halo groups, preferably selected from bromo, chloro and fluoro. Specifically embraced by the term "haloalkyl" are monohaloalkyl, dihaloalkyl and polyhaloalkyl groups. A monohaloalkyl group, for example, may have either a bromo, a chloro, or a fluoro atom within the group. Dihaloalkyl and polyhaloalkyl groups may be substituted with two or more of the same halo groups, or may have a combination of different halo groups. A dihaloalkyl group, for example, may have two bromo atoms, such as a dibromomethyl group, or two chloro atoms, such as a dichloromethyl group, or one bromo atom and one chloro atom, such as a bromochloromethyl group. Examples of a polyhaloalkyl are trifluoromethyl, 2,2,2-trifluoroethyl, perfluoroethyl and 2,2,3,3-tetrafluoropropyl groups. The terms "alkoxy" and "alkoxyalkyl" embrace linear or branched oxy-containing radicals each having alkyl portions of one to about ten carbon atoms, such as methoxy group.

Specific examples of alkyl groups are methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, n-pentyl,. iso-pentyl, methyl-butyl, dimethylbutyl and neopentyl. Typical alkenyl and alkynyl groups may have one unsaturated bond, such as an allyl group, or may have a plurality or unsaturated bonds, with such plurality of bonds either adjacent, such as allene-type structures, or in conjugation, or separated by several saturated carbons.

Included within the family of compounds of the described are the tautomeric forms of the described compounds, isomeric forms including diastereoisomers and individual enantiomers, and the pharmaceutically-acceptable salts thereof. The term "pharmaceutically-acceptable salts" embraces salts commonly used to form alkali metal salts and to form addition salts of free acids or free bases. Since the compounds contain basic nitrogen atoms, such salts are typically acid addition salts. The phrase "pharmaceutically-acceptable salts" is intended to embrace alkyl quaternary ammonium salts and n-oxides. The nature of the salt is not critical, provided that it is pharmaceutically acceptable, and acids which may be employed to form such salts are, of course, well known to those skilled in this art. Examples of acids which may be employed to form pharmaceutically acceptable acid addition salts include such inorganic acids as hydrochloric acid, sulfuric acid and phosphoric acid, and such organic acids as maleic acid, succinic acid and citric acid. Other pharmaceutically acceptable salts include salts with alkali metals or alkaline earth metals, such as sodium, potassium, calcium and magnesium, or with organic bases, such as dicyclohexylamine.

All of these salts may be prepared by conventional means by reacting, for example, the appropriate acid or base with the corresponding compound of the invention.

The compounds that are the subject of the invention herein can be prepared according to the following reaction schemes.

SCHEME 1

The preparation of compounds of formula I wherein the Ar group is A is shown in Scheme I. Compounds of formula I A are prepared starting from commercially available 2-aminonicotinic acid 1. Chloroacetaldehyde is reacted with 1 at elevated temperature in an alcoholic solvent (preferably EtOH at reflux) to afford compound 2A, which is converted to the acid chloride by conventional methods (preferably thionyl chloride/chloroform/dimethylformamide at reflux). This acid chloride 2B is then reacted with the appropriate amine 3 in the presence of a tertiary amine (preferably triethylamine) in a polar organic solvent (preferably dimethylformamide) to afford the desired compounds of formula IA. Alternatively, the imidazopyridine carboxylic acid 2A is reacted with the amine 3 using other acid-activating reagents (dicyclohexylcarbodiimide, iso-butylchloroformate, carbonyldiimidazole (CDI), etc.; preferably CDI in dimethylformamide at room temperature) to afford compounds of formula 1A.

Ring halogenated analogs of formula IA' are prepared according to scheme I. 2-Aminonicotinic acid 1 is converted to its methyl ester by conventional means. Treatment of this ester with halogenating reagents (NBS, NCS, C12, t-butylhypochlorite; preferably t-butylhypochorite/methanol/ room temperature) gives rise to the ring halogenated intermediate 4, which is converted to the imidazopyridine carboxylic acid ester 5A using conditions described above for the preparation of 2A. The corresponding imidazopyridine carboxylic acid 5 B is converted to compounds of formula IA' using reagents and conditions described above for the

preparation of I A from 2A.

SCHEME 2

The preparation of compounds of formulae IB, IC, ID, and IE are shown in scheme 2. In each case, the known acids 10 [EP 0254584A2, J. Medicinal Chemistry (1990), 33, 1924], 11 [EP 0289170A2, J. Medicinal Chemistry (1990), 33, 1924], 12 & 13 [EP 0289170A2, J. Medicinal Chemistry (1990), 33, 1929] are reacted with the appropriate amine or alcohol under conditions analogous to those described for scheme 1 or as described in EP 0254584A2 and EP 0289170A2.

SCHEME 3

The preparation of compounds of formula IF are shown in scheme 3. 2-Aminopyridine 14 is reacted with ethyl bromopyruvate 15 in an alcoholic solvent (preferably ethanol) to afford the imidazopyridine carboxylic acid ester 16A. Hydrolysis of the ester to the acid 16B occurs under conventional acid-catalyzed conditions. Conversion of 16B to amides and ester of formula IF is affected by employing one of a number of acid-activating reagents as sited above [preferably carbonyldiimidazole (CDI) in dimethylformamide at room temperature].

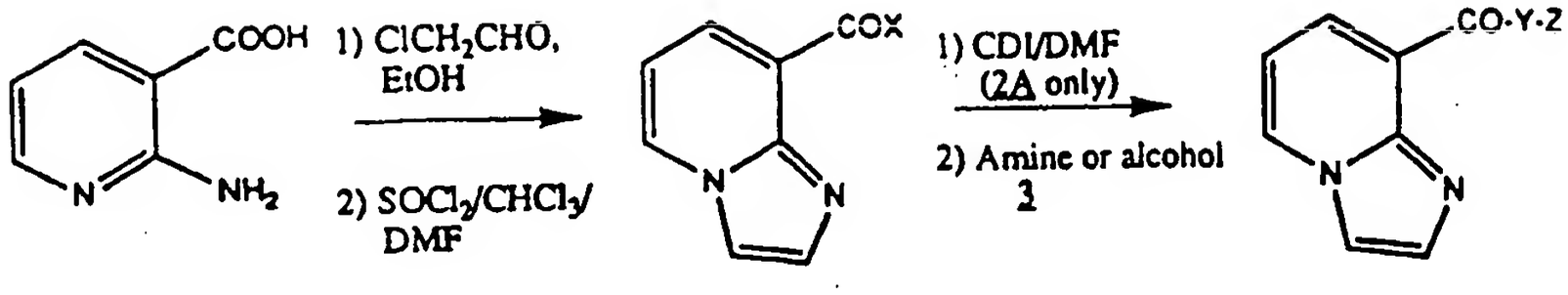
SCHEME 4

The preparation of compounds of formulae I-G and I-H are shown in Scheme 4. The known triazole aldehyde 17 [G. Jones et al., J. Chemical Society Perkin I (1981), 78] is oxidized by use of chromium trioxide/sulfuric acid or other conventional oxidizing agents to afford the triazole carboxylic acid 18. Coupling of 18 with the appropriate amine or alcohol 3 using conditions sited above [preferably CDI in dimethylformamide at room temperature] affords the desired triazoles of formula 1-G.

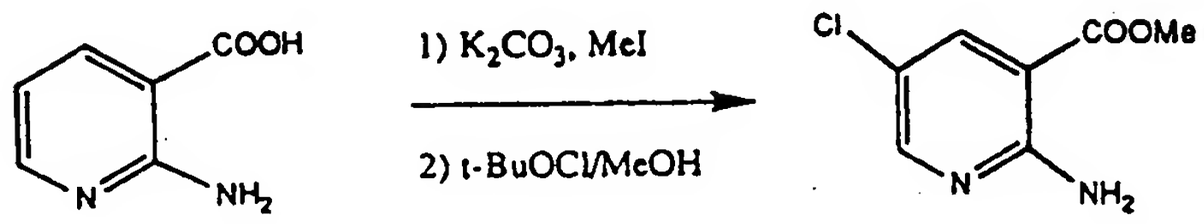
For preparation of compounds of formula I-H, the known lithiated compound 19 [B. Abarca et al, J. Chemical Society Perkin I (1985), 1897] is quenched with carbon dioxide or alkylhaloformate to afford 20B and 20A, respectively. 20A is converted to the acid 20B by conventional acid-catalyzed hydrolysis. Coupling of 20B with the appropriate amine or alcohol 3 is affected by using the conditions sited above [preferably CDI in dimethylformamide at room temperature] to afford the desired I-H. Alternatively, the appropriate amine 3 is converted to its carbamoyl halide 21 (Q = Cl, Br) or isocyanate 22. The lithiated species 19 is directly quenched with 21 or 22 to directly afford I-H (Y = NH).

These examples, as well as all examples herein, are given by way of illustration only and are not to be construed as limiting the invention, either in spirit or scope, as many modifications, both in materials and methods, will be apparent from this disclosure to those skilled in the art. In these examples, temperatures are given in degrees Celsius (°C) and quantities of materials in grams and milliliters unless otherwise noted.

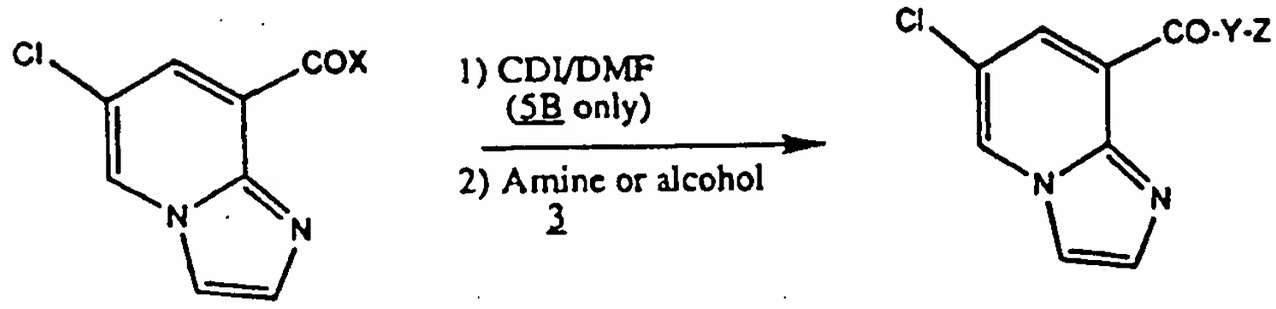
Scheme I: Preparation of Imidazopyridines (Ar group = A)



1 2A, X=OH 2B, X=Cl IA

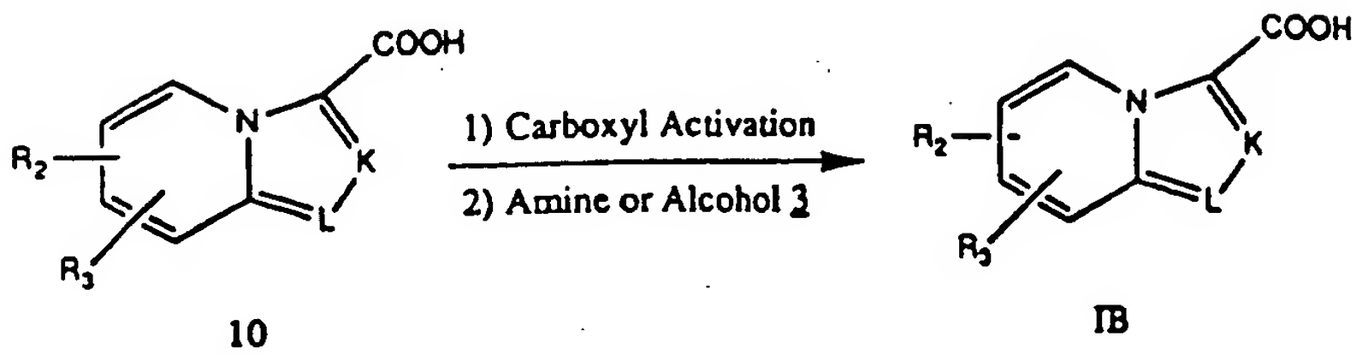


1 4

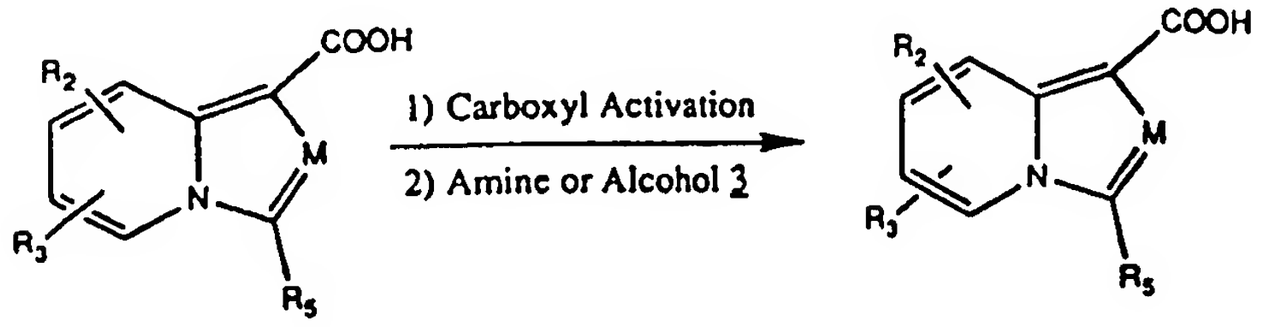


5A, X=OMe 5B, X=OH 5C, X=Cl IA'

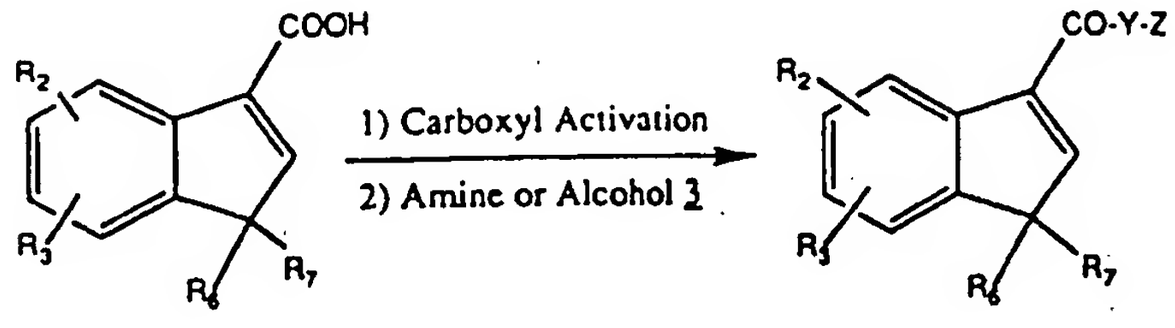
Scheme 2: Preparation of Compounds of Formulae IB, IC, ID and IE



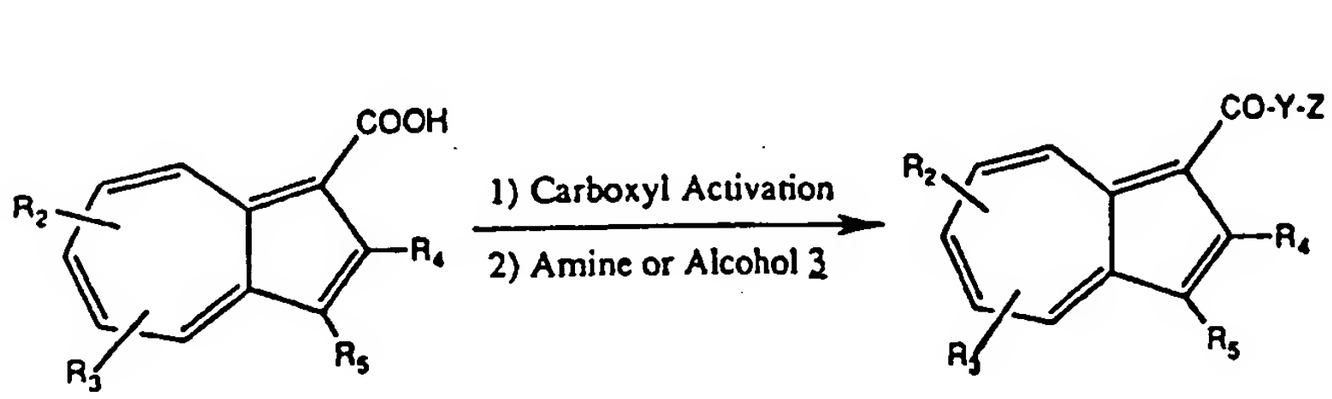
10 IB



11 IC

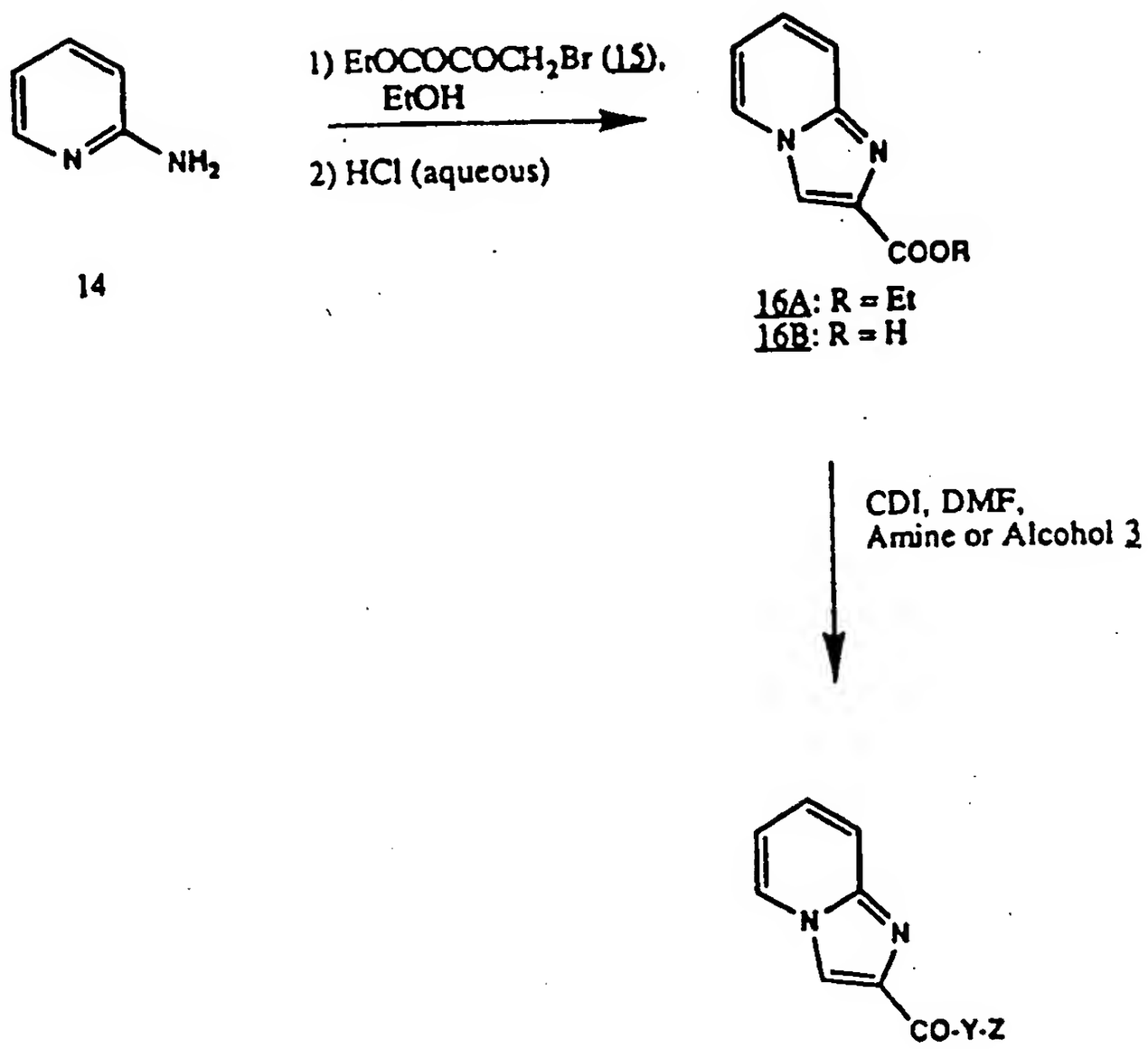


12 ID



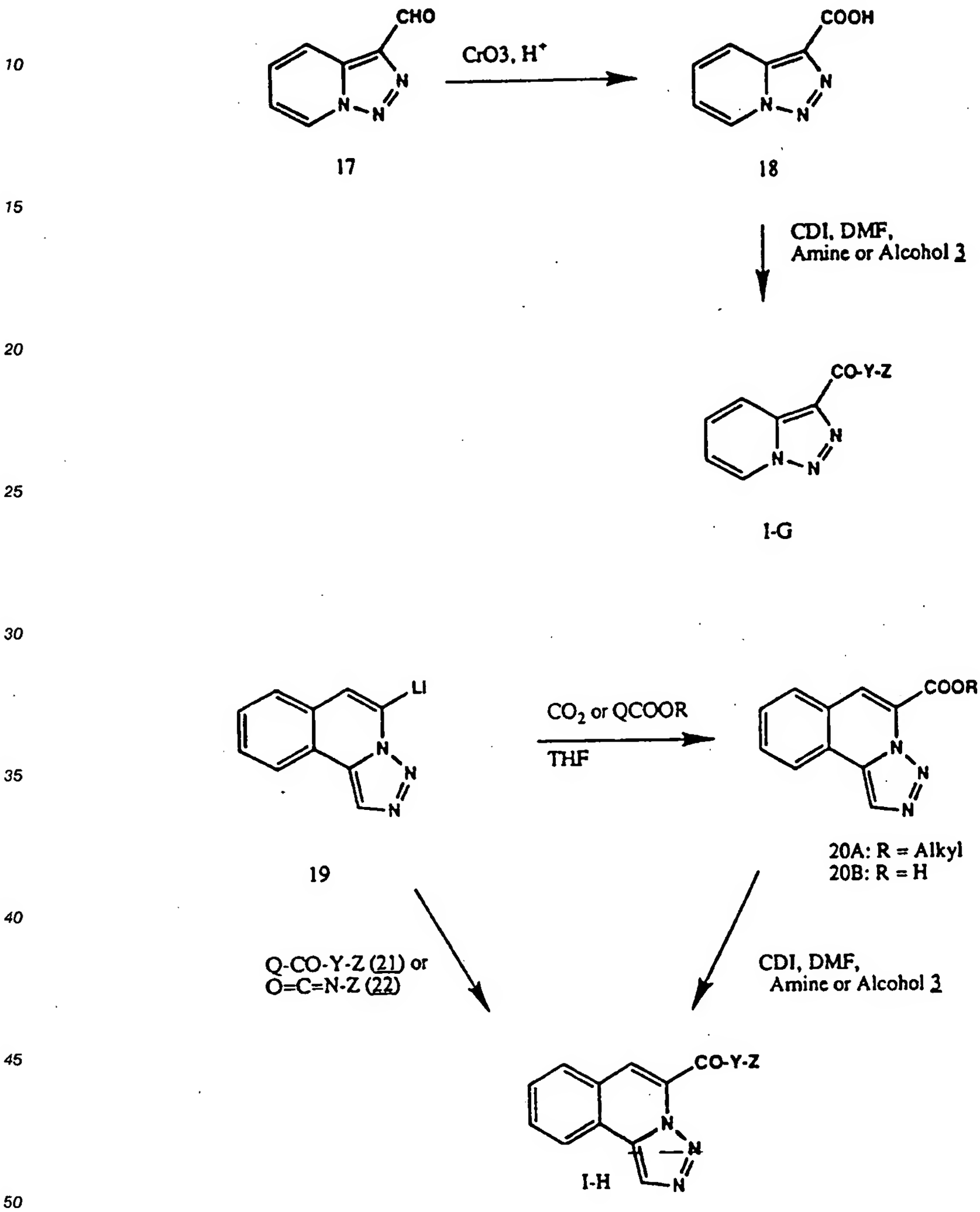
13 IE

SCHEME 3: Preparation of Compounds of Formula I-F.



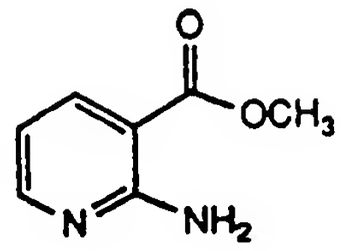
I-F

SCHEME 4: PREPARATION OF COMPOUNDS OF FORMULAE I-G AND I-H



Example A

(Methyl 2-aminonicotinate)



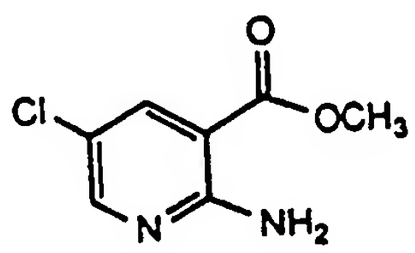
Procedure

The 2-aminonicotinic acid (5.0 g, 0.0362 mol) and K_2CO_3 (5.0 g, 0.0362 mol) were suspended in 50 ml of DMF and heated to reflux. Almost complete solution occurred. The mixture was cooled to 25° C and the CH_3I (5.1 g/2.2 ml, 0.0362 mol) was added and the mixture was stirred 18 hours. The mixture was filtered and concentrated. The residue was placed on a bed of silica and eluted with 5%/ EtOH/CH_2Cl_2/1/10% NH_4OH. The fractions containing the product were combined and concentrated. The residue was suspended in Et_2O, filtered and washed with Et_2O to yield 3.2 g (58%) the title compound.

Elements	Calc	Found	
Carbon	55.26	54.90	$C_7H_8N_2O_2$
Hydrogen	5.30	5.36	
Nitrogen	18.41	18.26	MW 152.15

Example B

(Methyl 2-amino-5-chloronicotinate)



Procedure

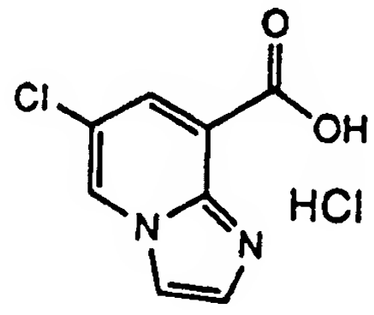
The compound of example A (800 mg, 0.00525 mol) was dissolved in MeOH (15 ml) and HCl gas was passed over the solution until the solution was acidic (pH 2). The solution was concentrated and the residue redissolved in MeOH (15 ml). The t-butylhypochlorite (570 mg, 0.00525 mol) was added and the reaction mixture stirred until the yellow color dissipated. Additional t-butylhypochlorite was added until tlc (5% EtOH/CH_2Cl_2/1/10% NH_4OH) indicated that the starting material was consumed.

The reaction mixture was concentrated and the residue dissolved in CH_2Cl_2. The organics were washed with 5% $NaHCO_3$ then 5% sodium thiosulfate. The organic layer was dried over $MgSO_4$ and concentrated to afford a solid. The solid was suspended in 1:1 CH_2Cl_2/hexane, filtered, washed with hexane and suction dried to yield 250 mg (26%) of the title compound m.p. 139-40° C.

Elements	Calc	Found	
Carbon	45.60	44.72	$C_7H_7ClN_2O_2$
Hydrogen	3.78	3.75	
Nitrogen	15.01	15.00	MW 186.60
Chlorine	19.00	19.20	

Example C

(6-Chloroimidazo[1,2-a]pyridine-8-carboxylic acid, monohydrochloride)



Procedure

The compound of example B (1.2 g, 0.0063 mol) and chloroacetaldehyde [45% aqueous solution (930 mg, 0.007 mol)] was heated to reflux in EtOH until tlc (5% EtOH/ CH_2Cl_2/1/10% NH_4OH) indicated that the reaction was complete. The solution was concentrated and the residue was suspended in acetone, filtered, washed with acetone, and air dried to yield 1.3 g (77%) of the methyl ester of the title compound m.p. 148-150° C (resolidify) 235-238° C (decomp).

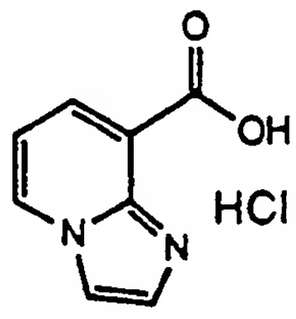
Elements	Calc	Found	
Carbon	40.50	40.58	$C_9H_7ClN_2O_2$ *1.05 HCl*1.0H_2O
Hydrogen	3.80	3.82	
Nitrogen	10.50	10.53	MW 266.92
Chlorine	27.23	27.43	

The methyl ester was heated to reflux in 15 ml of con HCl until tlc (5% EtOH/CH_2Cl_2/1/10% NH_4OH) indicated that the starting material was consumed. Concentration gave a residue which was suspended in acetone, filtered and dried to afford 1.15 g (99%) of the title compound: softens 275° C; m.p. 279-281° C (decomp).

Elements	Calc	Found	
Carbon	41.23	40.99	$C_8H_5ClN_2O_2$ *HCl
Hydrogen	2.60	2.53	
Nitrogen	12.02	11.95	MW 233.05
Chlorine	30.42	30.52	

Example D

(Imidazo[1,2-a]pyridine-8-carboxylic acid, monohydrochloride)



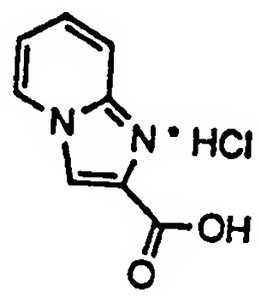
Procedure

Using 2-aminonicotinic acid (14.1 g, 0.102 mol) and chloroacetaldehyde [45% aqueous solution (8.6 g, 0.11 mol)], the same procedure as described above in example C was used. After workup 17.5 g (88%) of the title compound, m.p. 299-300° C (d comp), was isolated.

Elements	Calc	Found	
Carbon	48.38	48.16	$C_9H_7ClN_2O_2$ *1 HCl
Hydrogen	3.55	3.59	
Nitrogen	14.10	13.95	MW 198.61
Chlorine	17.85	17.50	

Example E

(Imidazo[1,2-a]pyridine-2-carboxylic acid monohydrochloride)



Procedure

2-aminopyridine (25.0 g, 0.128 mol) and ethyl bromopyruvate (12.0 g, 0.128 mol) were heated to reflux in EtOH (225 ml). The reaction mixture was concentrated and the residue partitioned between dilute K_2CO_3 and CH_2Cl_2. The organic layer was passed through a small bed of silica, eluting with .5% EtOH/CH_2Cl_2. The product eluted at the solvent front and this fraction was concentrated. The solid residue was suspended in Et_2O then filtered to yield 10.9 g (44%) of the ethyl ester of the title compound.

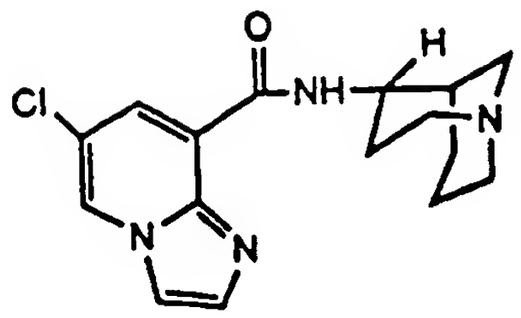
Elements	Calc	Found	
Carbon	62.56	62.79	$C_{10}H_{10}N_2O_2$ *.1 H_2O
Hydrogen	5.35	5.33	
Nitrogen	14.59	14.62	MW 192.00

The ethyl ester (5.0 g, 0.0256 moles) was refluxed in 50 ml of con HCl until tlc (5% EtOH/CH_2Cl_2/1/10% NH_4OH) indicated that the starting material was consumed. Concentration gave a residue which was suspended in acetone, filtered and dried to afford 5.2 g (95%) of the title compound.

Elements	Calc	Found	
Carbon	44.36	44.23	$C_8H_6N_2O_2$ *HCl
Hydrogen	4.19	4.17	
Nitrogen	12.93	12.77	MW 216.62
Chlorine	16.37	16.45	

Example 1

(endo-N-(1-Azabicyclo[3.3.1]nonan-4-yl)-6-chloroimidazo[1,2-a]pyridine-8-carboxamide, dihydrochloride)



•2HCl

Procedure

The compound of example C (1.1 g, 0.0047 mol) was suspended in $CHCl_3$/DMF (25 ml/3 drops). $SOCl_2$ (560 mg/0.338 ml, 0.0047 mol) was added and the mixture was heated to reflux with additional $SOCl_2$ added until tlc (5% EtOH/CH_2Cl_2/1/10% NH_4OH) indicated that the starting material was consumed. The mixture was concentrated in vacuo, azeotroping once with toluene.

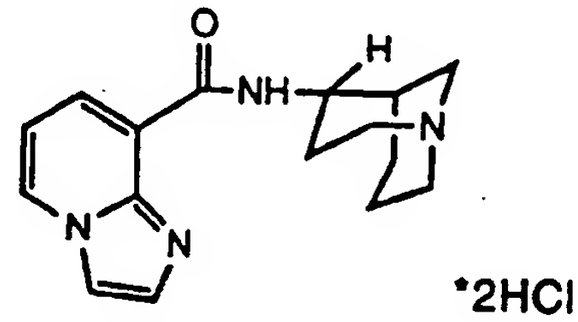
To the residue, dissolved in DMF (15 ml) and cooled in an ice bath, was added Et_3N (1.19 g/1.64 ml, 0.0118 mol) followed by endo-4-amino-1-azabicyclo[3.3.1]nonane (649 mg, 0.0047 mol) dissolved in 5 ml of DMF. The mixture was warmed to room temperature and stirred for 4 hours. Tlc (10% EtOH/CH_2Cl_2/1/10% NH_4OH) on basic alumnia indicated that the acid chloride was consumed. Concentration afforded a residue which was chromatographed on basic alumnia eluting with 1% EtOH/CH_2Cl_2/1/10% NH_4OH. The fractions containing the product were combined and concentrated in vacuo.

The residue was converted to the hydrochloride salt by dissolving in iPrOH and passing HCl gas over the solution. The solid was filtered, washed with iPrOH and dried in a vacuum desicator to yield 445 mg (20%) of the title compound, softens 230° C; m.p. 264-266° C (decomp).

Elements	Calc	Found	
Carbon	43.72	43.57	$C_{16}H_{19}ClN_4O$ *2.6 HCl*2.0H_2O *0.45 iPrOH
Hydrogen	6.17	5.80	
Nitrogen	11.58	11.40	MW476.68
Chlorine	26.77	26.52	

Example 2

(endo-N-(1-Azabicyclo[3.3.1]nonan-4-yl)imidazo[1,2-a]pyridine-8-carboxamide, dihydrochloride)



•2HCl

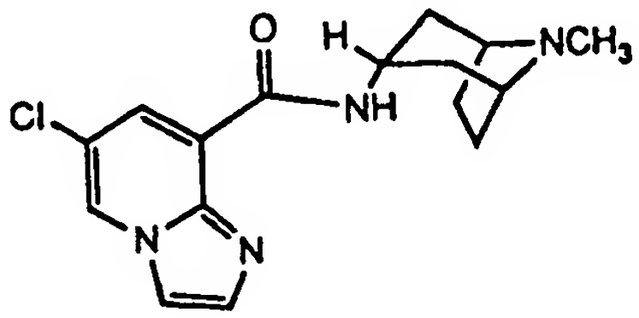
Procedure

Employing the compound of example D (1.4 g, 0.0071 mol), $SOCl_2$ (2.3 g/1.4ml, 0.02 mol), endo-4-amino-1-azabicyclo[3.3.1]nonane (1.0 g, 0.00713 mol), and Et_3N (2.5 g/3.84 ml, 0.0249 mo) dissolved in $CHCl_3$/DMF (25 ml/3 drops), the same procedure as described in example 1 was used. After workup 121 mg (5%) of the title compound was isolated.

Elements	Calc	Found	
Carbon	51.65	51.43	$C_{15}H_{20}N_4O$ *2 HCl*1/3H_2O*0.25 iPrOH
Hydrogen	6.79	6.38	
Nitrogen	15.30	15.12	MW 366.24
Chlorine	19.36	19.26	

Example 3

(endo-N-(8-Methyl-8-azabicyclo[3.2.1]octan-3-yl)-6-chloroimidazo[1,2-a]pyridine-8-carboxamide, dihydrochloride)



*2HCl

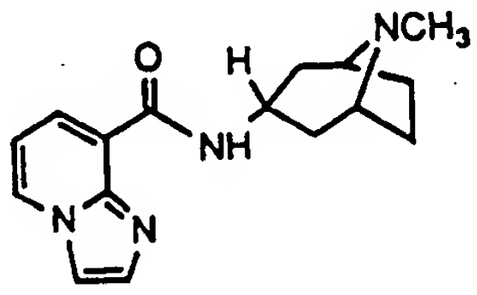
Procedure

The compound of example C (233 mg, 0.001 mol) and 1,1'-carbonyldiimidazole (241 mg, 0.0015 moles) were suspended in DMF (5 ml) and the mixture was stirred until solution occured (three hours). Endo-N-8-methyl-8-azabicyclo[3.2.1]-octane-3-amine[produced in accordance with the procedure in J. Am. Chem. Soc. 79, 4194(1957)] was added and the mixture was stirred for 18 hours. Tlc (30% EtOH/CH_2Cl_2/1/10% NH_4OH) indicated that the reaction was complete. Concentration afforded a residue which was purified by radial chromatography [(2 mm plate), gradient elution with 25% to 75% i-PrOH/CH_2Cl_2/1/10% NH_4OH]. Three components were collected. The desired was found in the third-eluted component. Concentration afforded a residue which was converted to the hydrochloride salt by dissolving in iPrOH and passing HCl gas over the solution. The solid was filtered, washed with iPrOH and dried in a vacuum desicator to yield 113 mg (25%) of the title compound.

Elements	Calc	Found	
Carbon	48.17	47.77	$C_{16}H_{19}ClN_4O$ *2 HCl *H_2O *0.75 iPrOH
Hydrogen	6.43	6.36	
Nitrogen	12.32	11.98	MW 454.82
Chlorine	23.38	23.18	

Example 4

(endo-N-(8-methyl-8-azabicyclo[3.2.1]octan-3-yl)imidazo[1,2-a]pyridine-8-carboxamide, hydrochloride)



* 1.1 HCl

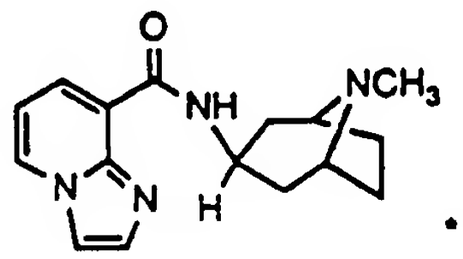
Procedure

The compound of example D (200 mg, 0.00101 mol) and 1,1'-carbonyldiimidazole (164 mg, 0.00101 mol) were suspended in the DMF (2 ml) and the mixture was stirred until solution occured (2.5 hours). Endo-N-8-methyl-8-azabicyclo[3.2.1]-octane-3-amine was added and the mixture was stirred for 48 hours. The mixture was concentrated to one half the original volume and EtOAc (2 ml) was added. The solid was filtered to afford (126 mg, 39%) the title compound.

Elements	Calc	Found	
Carbon	58.26	58.00	$C_{16}H_{20}N_4O$*1.1 HCl*0.3H_2O
Hydrogen	6.63	6.65	
Nitrogen	16.99	17.02	MW 329.67
Chlorine	11.82	11.90	
MS calcd for $C_{16}H_{20}N_4O$ 284.1637; found 284.1640.			

Example 5

(exo-N-(8-methyl-8-azabicyclo[3.2.1]octan-3-yl)imidazo[1,2-a]pyridine-8-carboxamide, hydrochloride)



* 1.1 HCl

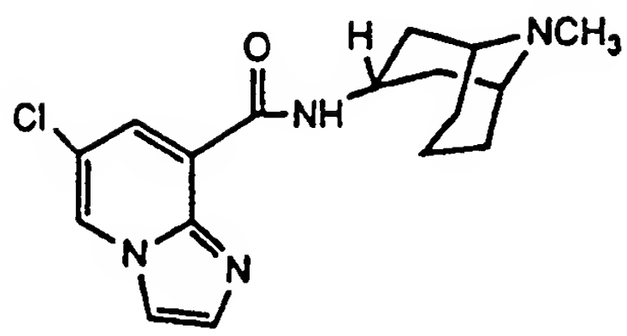
Procedure

The compound of example D (200 mg, 0.00101 mol) and 1,1'-carbonyldiimidazole (164 mg, 0.00101 mol) were suspended in DMF (2 ml) and the mixture was stirred until solution occured (2.5 hours). Exo-N-8-methyl-8-azabicyclo[3.2.1]octane-3-amine [prepared in accordance with the procedure in Berichte 31, 1202-(1898)] was added to the mixture and the resulting suspension was stirred for 4 days. EtOAc was added to the mixture and the solid filtered to afford (282 mg, 76%) the title compound.

Elements	Calc	Found	
Carbon	59.23	59.30	$C_{16}H_{20}N_4O$*1.1 HCl
Hydrogen	6.56	6.71	
Nitrogen	17.24	17.33	MW 324.47
Chlorine	12.02	11.85	
MS calcd for $C_{16}H_{20}N_4O$ 284.1637; found 284.1643.			

Example 6

(endo-N-(9-Methyl-9-azabicyclo[3.3.1]nonan-3-yl)-6-chloroimidazo[1,2-a]pyridine-8-carboxamide hydrochloride)



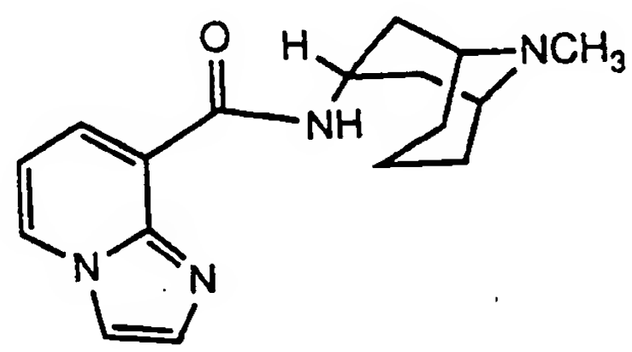
Procedure

The compound of example C (233 mg, 0.001 mol) and 1,1'-carbonyldiimidazole (178 mg, 0.001 mol) were suspended in DMF (5 ml), and the mixture was stirred for one hour before adding endo-N-9-methyl-9-azabicyclo[3.3.1]-nonane-3-amine (154 mg, 0.0011 moles). The mixture was stirred for 18 hours. Tlc (30% EtOH/CH_2Cl_2/1/10% NH_4OH) indicated that the reaction was complete. Concentration afforded a residue which was suspended in water and the pH adjusted to 11 with K_2CO_3. The solid was filtered and purified by radial chromatography [(2 mm plate), gradient elution 25% to 75% i-PrOH/CH_2Cl_2/1/10% NH_4OH]. Two components were collected. The desired product was found in the second-eluted component. Concentration afforded a residue which was converted to the hydrochloride salt by dissolving the residue in iPrOH then acetone and passing HCl gas over the solution. The solid was filtered, washed with i-PrOH then acetone and dried in a vacuum desicator to yield 168 mg (32%) of the title compound.

Elements	Calc	Found	
Carbon	45.57	45.36	$C_{17}H_{21}ClN_4O$ * 2.5 HCl * 2.5 H_2O * acetone
Hydrogen	6.60	6.68	
Nitrogen	10.63	10.61	MW 527.106
Chlorine	23.54	23.67	

Example 6A

(endo-N-(9-Methyl-9-azabicyclo[3.3.1]nonan-3-yl)-imdazo[1,2a]pyridine-8-carboxamide)



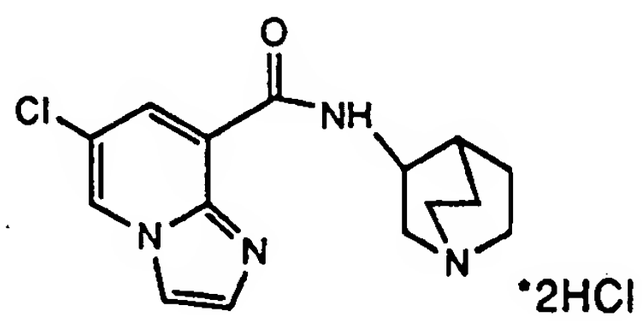
Procedure

The compound of Example D (198 mg, 0.001 moles) and 1,1'-carbonyldi-imidazole (178 mg, 0.001 moles) were suspended in the DMF (5 ml) and the mixture was stirred until solution occured (three hours). Endo-N-8-methyl-8-azabicyclo[3.2.1]-octane-4-amine and triethylamine (560 µl; 0.004 mole) were added and the mixture was stirred for 18 hours. Tlc 30% EtOH/CH_2Cl_2/1/10% NH_4OH indicated that the reaction was complete. Concentration afforded a residue which was purified by radial chromatography (2 mm plate), gradient elution with 200 ml portions of 10% i-PrOH/CH_2Cl_2/1/10% NH_4OH, 15, 20% i-PrOH (isopropylalcohol). Three components were collected. The desired was found in the third component. Concentration afforded a residue which was converted to the hydrochloride salt by dissolving the residue in i-PrOH and passing HCl gas over the solution. The solid was filtered, washed with i-PrOH and dried in a vacuum desicator to yield 133 mg (44.6%) of the title compound.

Elements	Calc	Found	
Carbon	53.45	53.75	$C_{17}H_{22}N_4O$ * 2.05 HCl *0.2 iPrOH
Hydrogen	6.93	6.59	
Nitrogen	15.01	14.79	MW 373.14
Chlorine	19.48	19.63	

Example 7

(N-(1-Azabicyclo[2.2.2]octan-3-yl)-6-chloroimidazo[1,2-a]pyridine-8-carboxamide dihydrochloride)



Procedure

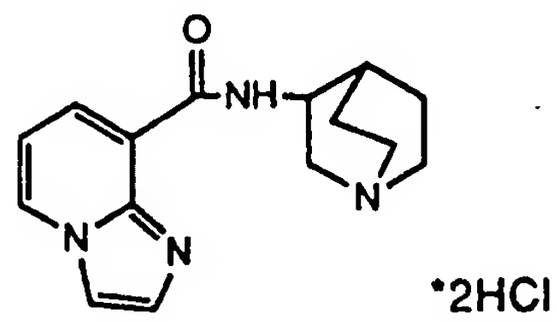
Using the compound of example C (233 mg, 0.001 moles), 1,1'-carbonyldiimidazole (241 mg, 0.0015 moles), and 3-aminoquinuclidine dihydrochloride (280 mg, 0.002 moles) in DMF (5 ml) the coupling was performed as discribed in example 3.

The residue was partitioned between dilute K_2CO_3 and CH_2Cl_2. The organic layer was separated, dried over $MgSO_4$ and concentrated to afford to an oil. The oil was purifed by silica gel chromatography [gradient elution with 20% to 100% iPrOH/CH_2Cl_2/1/10% NH_4OH]. The fractions containing the desired product were combined and concentrated to an oil which crystallized. The solid residue was converted to the hydrochloride salt by dissolving the residue in iPrOH and passing HCl gas over the solution. The solid was filtered, washed with iPrOH and dried in a vacuum desicator to yield 221 mg (56 %) of the title compound.

Elements	Calc	Found	
Carbon	45.55	45.95	$C_{15}H_{17}ClN_4O$ *2 HCl *H_2O
Hydrogen	5.35	5.13	
Nitrogen	14.16	14.45	MW 395.72
Chlorine	26.88	27.11	

Example 8

(N-(1-Azabicyclo[2.2.2]octan-3-yl)imidazo[1,2-a]pyridine-8-carboxamide, dihydrochloride)



Procedure

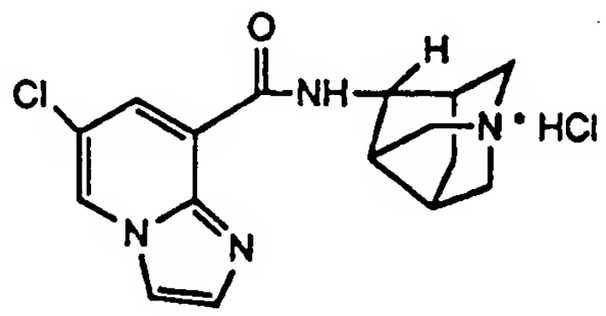
Employing the compound of example D (1.98 g, 0.01 mol), $SOCl_2$ (2.3 g/1.4ml, 0.02 mol), 3-

aminoquinuclidine dihydrochloride (200 mg, 0.01 mol), and Et_3N (4.0 g/5.6 ml, 0.04 mol) dissolved in $CHCl_3$/DMF (25 ml/3 drops) the same procedure as described in example 1 was used. After workup 2.2 mg (59%) of the title compound was isolated, m.p. 222° C (softens); 241-245° C (decomposes).

Elements	Calc	Found	
Carbon	50.88	50.73	$C_{15}H_{218}N_4O$ *2 HCl*0.25H_2O*0.75 iPrOH
Hydrogen	6.37	6.06	
Nitrogen	15.07	15.40	MW 371.79
Chlorine	19.07	18.83	

Example 9

((±)-endo-N-(Hexahydro-1H-2,5β-methano-3aα,6aα-cyclopenta[c]pyrrol-4α-yl)-6-chloroimidazo[1,2-a]pyridine-8-carboxamide, monohydrochloride)



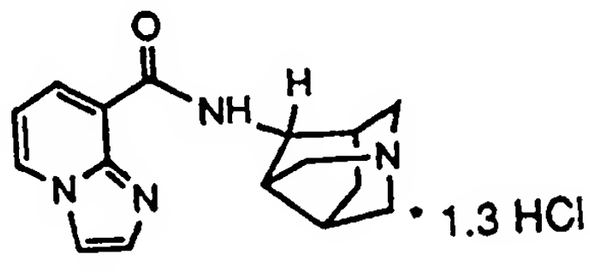
Procedure

The compound of example C (115 mg, 0.0005 mol) and 1,1'-carbonyldiimidazole (86 mg, 0.000525 mol) were suspended in DMF (2.5 ml), and the mixture was stirred for one hour before adding (±)-endo-N-hexahydro-1H-2,5β-methano-3aα,6aα-cyclopenta[c]pyrrol-4α-amine [U.S. Patent Appl. serial no. 07/515,391] (69 mg, 0.0005 mol). A solid precipitated from solution. The mixture was stirred for an additional hour. The solid was filtered, washed with acetone, and dried to yield 97 mg (52%) of the title compound.

Elements	Calc	Found	
Carbon	51.76	51.81	$C_{16}H_{17}ClN_4O$ *HCl *H_2O
Hydrogen	5.43	5.24	
Nitrogen	15.09	15.27	MW 371.27
Chlorine	19.10	19.47	

Example 10

((±)-endo-N-(Hexahydro-1H-2,5β-methano-3aα,6aα-cyclopenta[c]pyrrol-4α-yl)imidazo[1,2-a]pyridine-8-carboxamide, hydrochloride)



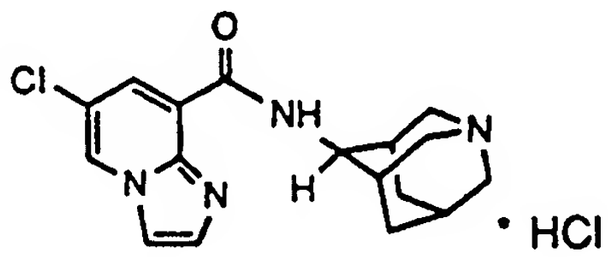
Procedure

The compound of example D (53 mg, 0.00027 mol) and 1,1'-carbonyldiimidazole (43 mg, 0.00027 mol) were suspended in DMF (2 ml), and the suspension was stirred for 4.5 h. (±)-Endo-N-hexahydro-1H-2,5β-methano-3aα,6aα-cyclopenta[c]pyrrol-4α-amine was added and the mixture was stirred for 16 h. The mixture was diluted with EtOAc and the solid filtered to afford (46 mg, 58%) the title compound.

Elements	Calc	Found	
Carbon	58.28	58.17	$C_{16}H_{18}N_4O$*1.3HCl
Hydrogen	5.90	5.97	
Nitrogen	16.99	17.04	MW 329.54
MS calcd for $C_{16}H_{218}N_4O$ 282.1480; found 282.1472.			

Example 11

(exo-N-(1-azatricyclo[3.3.1.1^{3,7}]decan-4-yl)-6-chloroimidazo[1,2-a]pyridine-8-carboxamide, monohydrochloride)



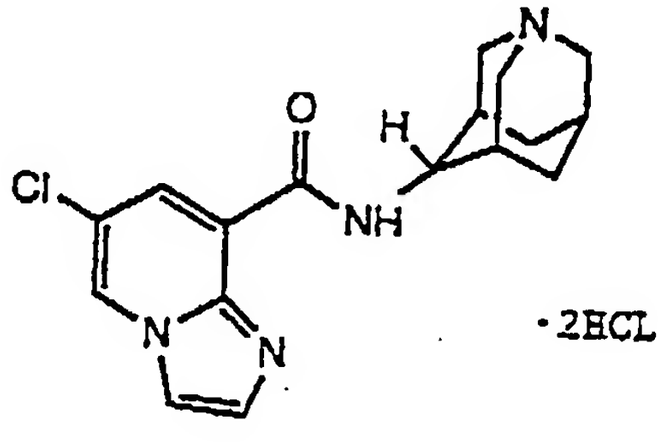
Procedure

The compound of example C (150 mg, 0.00064 mol) and 1,1'-carbonyldiimidazole (104 mg, 0.00064 mol) were suspended in DMF (1 ml), and the suspension was stirred for 2 h. A solution of exo-N-(1-azatricyclo[3.3.1.1^{3,7}]decane-4-amine in DMF (1 ml) was added and the mixture was stirred for 16 h. The mixture was diluted with EtOAc (4 ml). The solid was filtered to afford 226 mg of a solid which was recrystallized from MeOH to yield (139 mg, 59%) the title compound.

Elements	Calc	Found	
Carbon	55.60	55.20	$C_{17}H_{19}ClN_4O$ *1 HCl
Hydrogen	5.49	5.51	
Nitrogen	15.41	15.26	MW 367.26
Chlorine	19.31	19.59	

Example 11A

(1α,3β,5α,7β-1-azatricyclo[3.3.1.1^{3,7}]decan-4β-7yl)-6-chloroimidazo[1,2-a]pyridine-8-carboxamide dihydrochloride



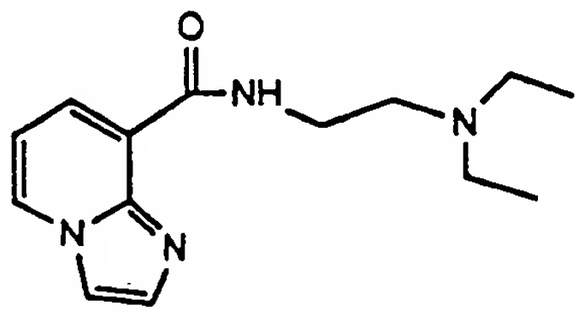
Procedure

The compound of Example C (153 mg, 0.00065 moles) and 1,1'-carbonyldi-imidazole (106 mg, 0.00065 moles) were suspended in the DMF (2.5 ml) and the mixture was stirred until solution occured (three hours). At this time, 1α,3β,5α,7β-1-azatricyclo[3.3.1.1^{3,7}]decan-4β-amine and triethylamine (280 μl; 0.002 mole) were added and the mixture was stirred for 18 hours. Tlc 30% EtOH/CH_2Cl_2/1/10% NH_4OH indicated that the reaction was complete. Concentration afforded a residue which was partitioned between dilute K_2CO_3 and $CHCl_3$. The organic layer was dried over $MgSO_4$ and concentrated. The residue was recrystalized from i-PrOH/HCl. The solid was filtered, washed with i-PrOH and dried in a vacuum desicator to yield 113 mg (39%) of the title compound.

Elements	Calc	Found	
Carbon	49.68	49.97	$C_{17}H_{19}ClN_4O$*2HCl *0.75 H_2O *0.5 i-PrOH
Hydrogen	5.97	5.84	
Nitrogen	12.53	12.39	MW 447.30
Chlorine	23.78	23.78	

Example 12

(N-[2-(Diethylamino)ethyl]imidazo[1,2-a]pyridine-8-carboxamide)



*.25 H_2O

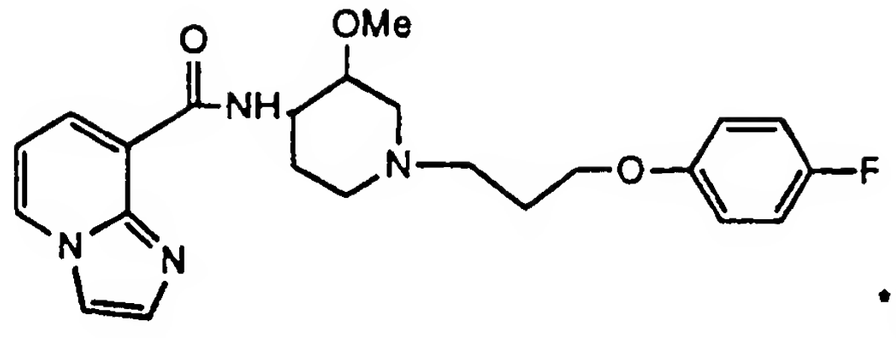
Procedure

Employing the compound of example D (1.98 g, 0.01 mol), $SOCl_2$ (2.3 g/1.4ml, 0.02 mol), N,N-diethylenediamine (1.27 g, 0.011 mol), and Et_3N (2.0 g/2.8 ml, 0.02 mol) dissolved in $CHCl_3$/DMF (25 ml/3 drops), the same procedure as described in example 1 was used. After workup 610 mg (23%) of the title compound was isolated as an oil.

Elements	Calc	Found	
Carbon	63.49	63.54	$C_{14}H_{20}N_4O$ *.25H_2O
Hydrogen	7.80	7.55	
Nitrogen	21.16	20.99	MW 264.83

Example 13

(Cis-N-[[3-(4-Fluorophenoxy)propyl]-3-methoxy-4-piperidinylamine]imidazo[1,2-a]pyridine-8-carboxamide)



• 2.4 HCl

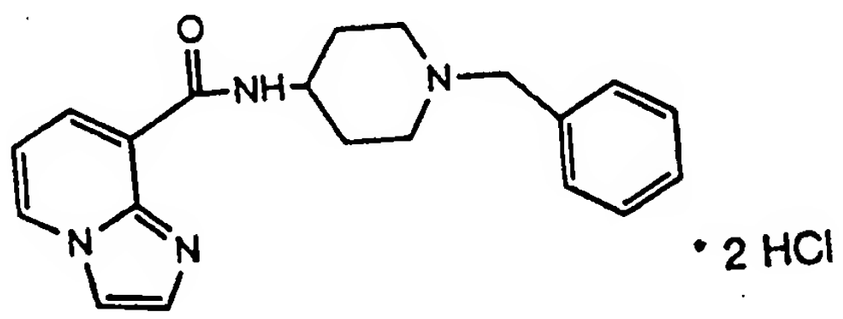
Procedure

Employing the compound of example D (1.98 g, 0.01 mol), $SOCl_2$ (2.3 g/1.4ml, 0.02 mol), cis-1-[3-(4-fluorophenoxy)propyl]-3-methoxy-4-pipendinylamne (3.1 g, 0.011 mol), and Et_3N (3.5 g/3.84 ml, 0.035 mol) dissolved in $CHCl_3$/DMF (25 ml/3 drops), the same procedure as described in example 1 was used. After workup 2.29 mg (42%) of the title compound was isolated.

Elements	Calc	Found	
Carbon	50.64	50.74	$C_{23}H_{29}FN_4O_3$ *2.4 HCl *1.75H_2O
Hydrogen	6.08	5.69	
Nitrogen	10.27	10.44	MW 545.53
Chlorine	15.60	15.44	

Example 14

(N-[1-(Phenylmethyl)-4-piperidinyl]imidazo[1,2-a]pyridine-8-carboxamide, dihydrochloride)



• 2 HCl

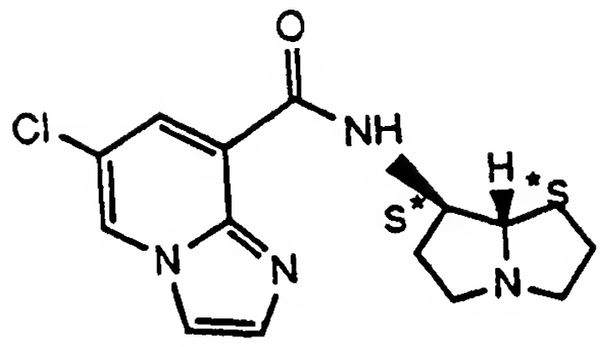
Procedure

Employing the compound of example D (1.98 g, 0.01 moles), $SOCl_2$ (2.3 g/1.4 ml, 0.02 mol), 4-amino-1-benzylpiperidine (2.0 g, 0.011 mol), and Et_3N (3.5 g/4.89 ml, 0.035 mol) dissolved in $CHCl_3$/DMF (25 ml/3 drops), the same procedure as described in example 1 was used. After workup 3.1 g (72%) of the title compound was isolated, m.p. 290-291 ° C (decomposes).

Elements	Calc	Found	
Carbon	56.01	56.32	$C_{20}H_{22}N_4O_3$ *2 HCl *.5H_2O
Hydrogen	5.99	5.94	
Nitrogen	13.06	12.67	MW 383.92
Chlorine	16.53	16.54	

Example 14A

N-exo((4-s,7α-s)-tetrahydro-1H-pyrrolizin-4(5H)-yl)-6-chloroimidazo[1,2-a]pyridine-8-carboxamide dihydrochloride



Procedure

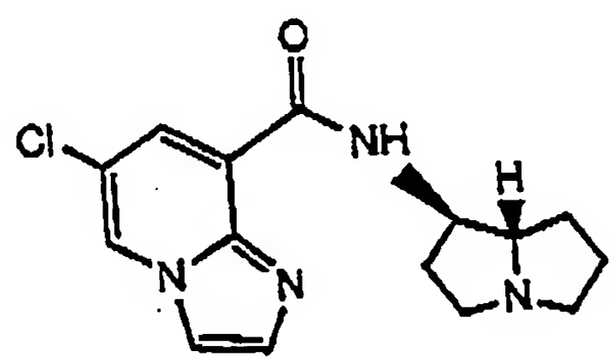
The acid of the compound of Example B (118 mg, 0.00051 moles) and 1,1'-carbonyldi-imidazole (70 mg, 0.00051 moles) were suspended in the DMF (1 ml) and the mixture was stirred until solution occured (three hours). At this time, exo(4-s,7α-s)-tetrahydro-1H-pyrrolizin-4-amine (70 mg; 0.000499 moles) and triethylamine (280 μl; 0.002 mole) were added and the mixture was stirred for 18 hours. Tlc 30% EtOH/CH_2Cl_2/1/10% NH_4OH indicated that the reaction was complete. Concentration afforded a residue which was purified by prep tlc chromatography, elution with 30% MeOH/CH_2Cl_2/1/10% NH_4OH to yield 182 mg (90%) of the pyridine derivative.

This compound (120mg; 0.00045 moles) was combined with chloroacetaldehyde (45% in H_2O)(142mg; 0.0009 moles) in EtOH (10 ml) and refluxed until tlc 30% EtOH/CH_2Cl_2/1/10% NH_4OH indicated that the reaction was complete. Concentration afforded a residue which was purified by prep tlc chromatography, elution with 30% MeOH/CH_2Cl_2/1/10% NH_4OH to yield 105 mg (73%) of the product. The residue was converted to the HCl salt with MeOH/HCl.

Elements	Calc	Found	
Carbon	42.24	42.43	$C_{15}H_{18}ClN_4O$*2.35 HCl*2.75 H_2O 0.25 MeOH
Hydrogen	6.08	6.01	
Nitrogen	12.13	12.13	MW 462.04
Chlorine	25.70	25.72	

Example 14B

N-exo(tetrahydro-1H-pyrrolizin-4(5H)-yl)-6-chloroimidazo[1,2-a]pyridine-8-carboxamide dihydrochloride



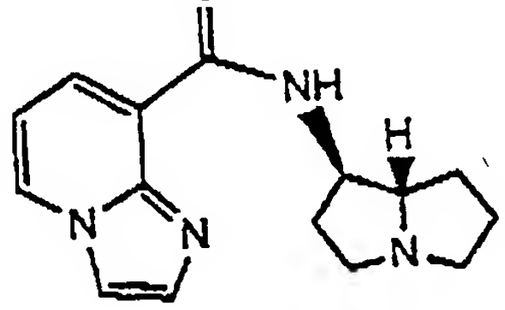
Procedure

The compound of Example D (198 mg, 0.001 moles) and 1,1'-carbonyldi-imidazole (178 mg, 0.0011 moles) were suspended in the DMF (5 ml) and the mixture was stirred until solution occured (three hours). At this time, exo-tetrahydro-1H-pyrrolizin-4(5H)-amine and triethylamine (560 μl; 0.004 mole) were added and the mixture was stirred for 18 hours. Tlc 30% EtOH /CH_2Cl_2/1/10% NH_4OH indicated that the reaction was complete. Concentration afforded a residue which was partitioned between dilute K_2CO_3 and $CHCl_3$. The organic layer was dried over $MgSO_4$ and concentrated. The residue was recrystalized from i-PrOH/HCl. The solid was filtered, washed with i-PrOH and dried in a vacuum desicator to yield 244 mg (60%) of the title compound.

Elements	Calc	Found	
Carbon	47.24	47.58	$C_{15}H_{17}ClN_4O$ * 2 HCl *0.50 H_2O *0.33 i-PrOH
Hydrogen	5.61	5.47	
Nitrogen	13.78	13.60	MW 406.54
Chlorine	26.16	26.03	

Example 14C

N-exo(tetrahydro-1H-pyrrolizin-4(5H)-yl)imidazo[1,2-a] pyridine-8-carboxamide dihydrochloride



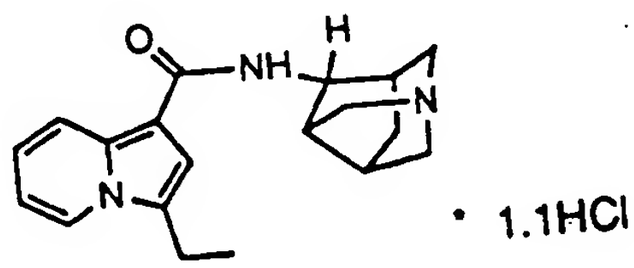
Procedure

The compound of Example D (233 mg, 0.001 moles) and 1,1'-carbonyldi-imidazole (178 mg, 0.0011 moles) were suspended in the DMF (5 ml) and the mixture was stirred until solution occured (three hours). Exo-tetrahydro-1H-pyrrolizin-4(5H)-amine and triethylamine (563 µl; 0.004 mole) were added and the mixture was stirred for 18 hours. Tlc 30% EtOH/CH_2Cl_2/1/10% NH_4OH indicated that the reaction was complete. Concentration afforded a residue which was purified by radial chromatography (2 mm plate), gradient elution with 200 ml portions of 10% i-PrOH/CH2Cl_2/1/10% NH_4OH, 15, 20% i-PrOH. The residue was crystalized from i-PrOH/HCl. The solid was filtered, washed with i-PrOH and dried in a vacuum desicator to yield 176 mg (48%) of the title compound.

Elements	Calc	Found	
Carbon	49.62	49.23	$C_{15}H_{18}N_4O$ * 2.05 HCl *H20
Hydrogen	6.12	6.11	
Nitrogen	15.43	15.33	MW 363.10
Chlorine	20.02	19.94	

Example 15

((±)-endo-N-(Hexahydro-1H-2,5β-methano-3aα,6aα-cyclopenta[c]pyrrol-4aα-yl)-3-ethylindolizine-1-carboxamide monohydrochloride)



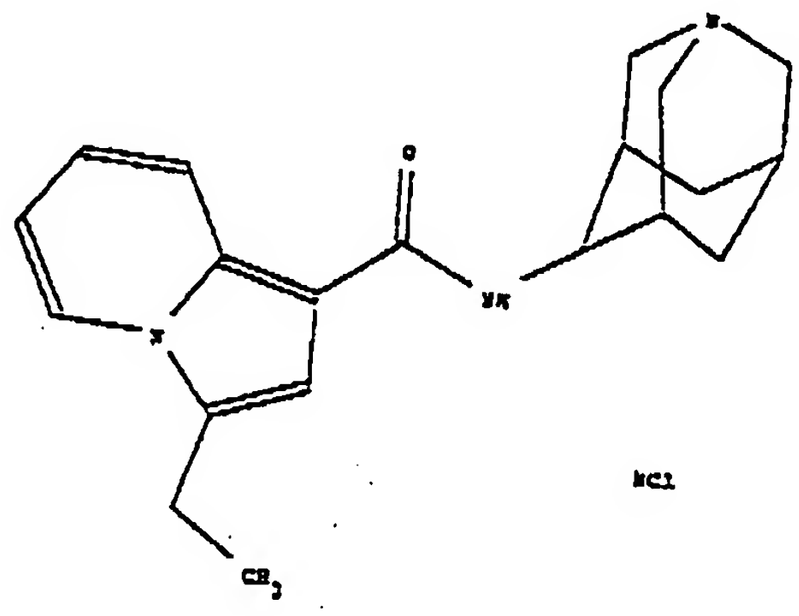
Procedure

3-Ethylindolizine-1-carboxylic acid (76.7 mg, 0.000405 mol) [prepration described by Bermudez et al. in Journal of Medicinal Chemistry (1990)33: 1928] and 1,1'-carbonyldiimidazole (65.7 mg, 0.000405 mol) were suspended in DMF (5 ml) and the mixture was stirred for 4 h. (±)-Endo-N-(Hexahydro-1H-2,5β-methano-3aα,6aα-cyclopenta[c]pyrrol-4α-amine (56 mg, 0.000405 mol) in DMF (1 ml) was added and the mixture stirred an additional 22h. An additional premixed portion of 3-ethylindolizine-1-carboxylic acid (38 mg, 0.20 mmol) and 1,1'-carbonyldiimidazole (33 mg, 0.20 mmol) in DMF (1 ml) was added. This mixture was stirred for an additional 16 h. The reaction mixture was concentrated in vacuo to give a residue which was treated with 20% K_2CO_3 (1 ml) and extracted with $CHCl_3$ (3X). The combined extracts were washed with water and brine and dried over Na_2SO_4. Concentration in vacuo gave 74 mg of an oil which was chromatographed on silica gel eluting with 3/97 MeOH(NH_3)/$CHCl_3$ to give the desired amide (21.4 mg, 17%) as the free base. The free base was converted to the hydrochloride salt by dissolving in HCl/MeOH [prepared from acetyl chloride (4.9 μl, 0.069 mmol) and MeOH (1 ml)]. Concentration in vacuo gave the desired hydrochloride salt (24.2 mg) as a solid.

Elements	Calc	Found	
Carbon	60.61	60.55	$C_{19}H_{23}N_3O$ *1.1 HCl *1.5H_2O
Hydrogen	7.25	6.80	
Nitrogen	11.16	11.06	MW 376.31
MS calcd for $C_{19}H_{23}N_3O$: 309.1841; found 309.1845.			

Example 15A

(1α,3β,5α,7β-1-azatricyclo[3.3.1.1^{3,7}]decan-4β-yl)-3-ethylindolizine-1-carboxamide monohydrochloride



Procedure

3-ethylindolizine-1-carboxylic acid (190 mg, 1.0 mmole) was dissolved in $CHCl_3$ (dry), oxalyl chloride (184 μl, 2.1 mmole) was added and the mixture stirred for 2 hours. Concentration in vacuo gave a solid, which was redissolved in $CHCl_3$ (5 ml)/DMF (.3 mls). A solution of endo-N-(1-azatricyclo[3.3.1.1.] decane-4 amine (140 mg, .92 mmole), triethyl amine [280 μl, 2.0 mmole) in $CHCl_3$ (2 ml) was added. The mixture was stirred for 18 hours. The organic layer was washed with 1N NaOH, brine and dried over K_2CO_3. Filtration and concentration in vacuo afforded .420 mg of a solid which was chromatographed on silica gel eluting with 8% CH_3OH (NH_3†)/$CHCl_3$ to give the title compound (197 mg, 66%) as the free base.

Calculated MS for $C_{20}H_{25}N_3O$: 323.20
Found: 323.199

DSC = 188.12 - 191.72°C @ 82.5 5/g.

And: Calculated for $C_{20}H_{25}N_3O$.$2H_2O$: C, 73.45; H, 7.83; N, 12.85
Found: C, 73.32; H, 7.80;

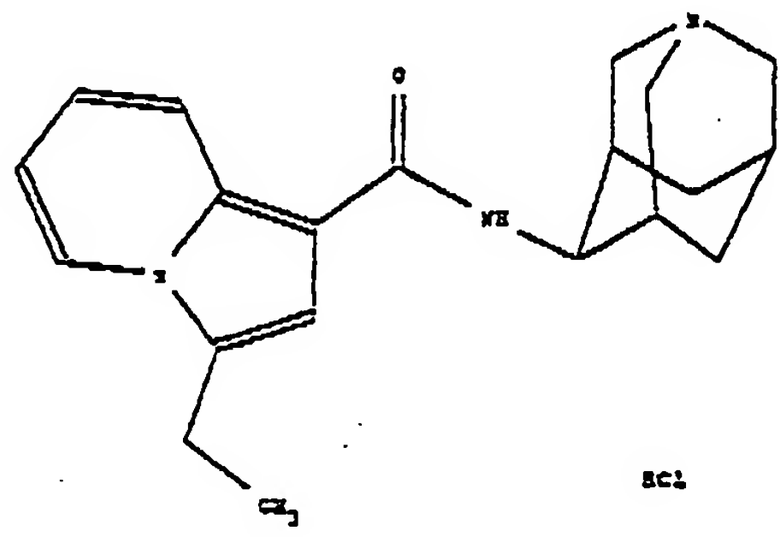
N, 12.70

The HCl salt was made by adding acetyl chloride (87µl, 1.22 mmole) to CH_3OH (1 ml) stirring for 25 minutes, and addition of the free base (197 mg, .609 mole). The solution was stirred 1 hour. Concentration in vacuo to about .4 ml and addition of Et_2O(200 ml) gave a solid was filtered and dried under vacuum to yield 182 mg (83%) of the title compound.

Calculated for $C_{20}H_{25}N_3O \cdot HCL.4H_2O$	
	Found
C, 65.44 H, 7.36 N, 11.45 Cl, 9.66	65.66 7.20 11.21 9.91
Calculated HRMS for $C_{20}H_{25}N_3O$ = 323.42 Found = 323.1986	

Example 15B

(1α,3β,5α,7β-1-azatricyclo[3.3.1.1^{3,7}]decan-4α-yl)-3-ethylindolizine-1-carboxamide monohydrochloride



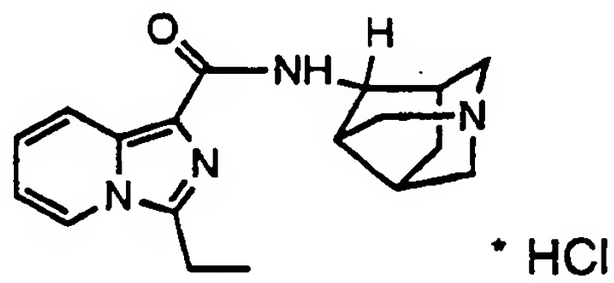
Procedure

To 3-ethylindolizine-1-carboxylic acid (190 mg, 1.0 mmole) in dry $CHCl_3$ was added oxalyl chloride (184 µl, 2.1 mmole) and the resulting solution was stirred for 2 hours. Concentrated in vacuo gave a solid which was dissolved in $CHCl_3$ (5 mls)/DMF (.3 mls) and to the resulting solution was then added a solution of exo-N-(1-azatricyclo[3.3.1.1.] decane-4-amine (140 mgs, .92 mmole) and triethyl amine [280 µl, 2.0 mmole) in $CHCl_3$ (2 mls). The solution was then stirred for 18 hours. The $CHCl_3$ layer was then washed with 1N NaOH, brine and dried over K_2CO_3, filtered, and concentrated in vacuo to give a solid. The solid was chromatographed on silica gel eluting with 8% CH_3OH (NH_3†)/$CHCl_3$ to give 280 mg (70.5%) as the free base. The hydrochloride salt was made by the same procedure as in Example 15A to give 192 mg (85%) solid.

Calculated for $C_{20}H_{25}N_3O.HCl. .35H_2O$	
	Found
C, 65.50 H, 7.35 N, 11.47 Cl, 9.68	65.96 7.57 11.08 9.70
Calculated MS for $C_{20}H_{25}N_3O$ = 323.420 Found 323.196	

Example 16

((±)-endo-N-(Hexahydro-1H,2,5β-methano-3aα,6aα-cyclopenta[c]pyrrol-4α-yl)-3-ethylimidazo[1,5-a]pyridine-1-carboxamide, monohydrochloride)

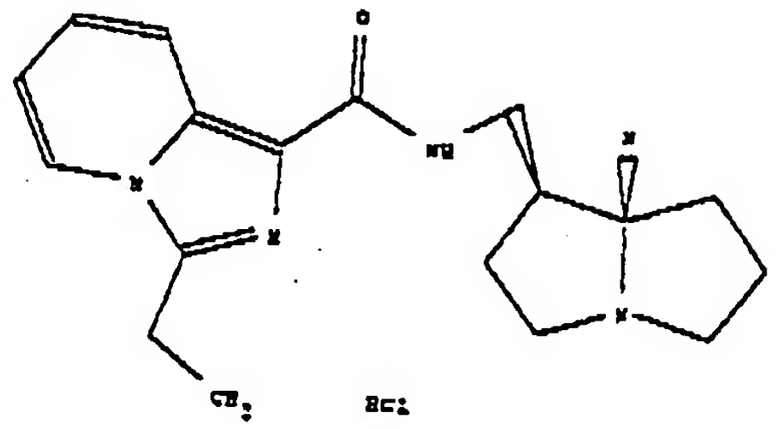


Procedure

3-Ethylimidazo[1,5-a]pyridine-1-carboxylic acid (72.9 mg, 0.00038 mol) [prepration described by Bermudez et al. in Journal of Medicinal Chemistry, (1990)33, 1928] and 1,1'-carbonyldi-imidazole (62 mg, 0.00038 mol) were suspended in DMF (0.5 ml) and the mixture was stirred for 4 h. (±)-Endo-N-(Hexahydro-1H-2,5β-methano-3aα,6aα-cyclopenta[c]pyrrol-4α-amine (53 mg, 0.00038 mol) in DMF (1 ml) was added and the mixture stirred an additional 40h. The reaction mixture was concentrated in vacuo to give a residue which was treated with 20% K_2CO_3 (1 ml) and extracted with $CHCl_3$ (3X). The combined extracts were washed with water and brine and dried over Na_2SO_4. Concentration in vacuo gave 127 mg of a solid which was chromatographed on silica gel eluting with 2/98 MeOH (NH_3)/$CHCl_3$ to give the desired amide (43 mg, 36%) as the free base. The free base was converted to the hydrochloride salt by dissolving in NCl/MeOH [prepared from acetyl chloride (8.8 µl, 0.00014 mol) and MeOH (1 ml)]. Addition of this methanolic solution to diethyl ether (75 ml) and filtration gave the title compound as the hydrochloride salt (39 mg).
MS calcd for $C_{18}H_{22}N_4O$: 310.1793; found 310.1791.

Example 16A

N-exo(tetrahydro-1H-pyrrolizin-4(5H)-ylmethyl)-3-ethyl-imidazo[1,2-a]pyridine-1-carboxamide monohydrochloride



Procedure

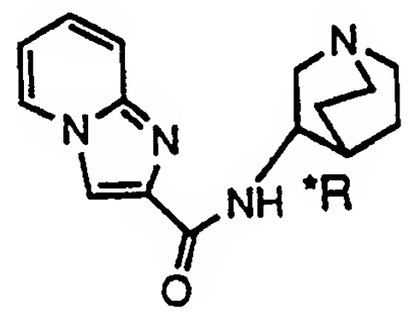
3-ethylimidazo[1,5-a]pyridine-1-carboxylic acid (190 mg, 1.0 mmole) was suspended in $CHCl_3$ (2 ml). Oxalyl chloride (184 µl, 2.1 mmole) and DMF (1 drop) were added and mixture stirred for 2 hours. Reaction mixture was concentrated in vacuo, azeotroping once with toluene.

The residue dissolved in $CHCl_3$ was added a solution of exo-tetrahydro-1H-pyrrolizin-4(5H)-methylamine (140 mg, 1.0 mmole), triethyl amine (279 µl, 2.0 mmole) in $CHCl_3$ (2 ml) and the mixture stirred for 18 hours. Organic solution was washed with 1N NaOH, brine, dried over K_2CO_3, filtered and concentrated to give a crude oil. Oil was chromatographed on silica gel eluting with 5% $CH_3OH(NH_3$ †) $CHCl_3$ to give 110 mg (35%) of desired compound as the free base. HCl salt was made by same method as in Example 15A.

Calculated for $C_{18}H_{24}N_4O.HCl.3/4\ H_2O$		
C, 57.91	58.15	calculated MS
H, 7.24	6.95	for $C_{18}H_{24}N_4O$
N, 15.01	14.95	312.42
Cl, 12.35	12.25	Found 312.195

Example 17

(R-N-(1-Azabicyclo[2.2.2]octan-3-yl)imidazo[1,2-a]pyridine-2-carboxamide dihydrochloride)



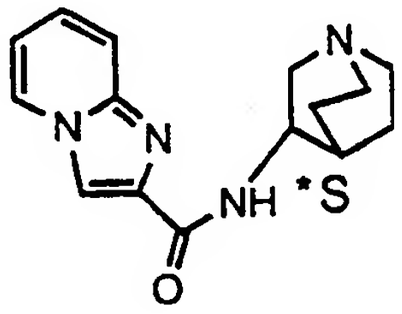
Procedure

The compound of example E (216 mg, 0.001 mol) and 1,1'-carbonyldiimidazole (178 mg, 0.001 mol) were suspended in DMF (5 ml), and the mixture was stirred for 1 h before adding R-3-aminoquinuclidinedihydrochloride (200 mg, 0.001 mol), synthesized using the procedure in European Patent #0280 603. The mixture was stirred for 18 hours. Tlc (30% EtOH/CH_2Cl_2/1/10% NH_4OH) indicated that the reaction was complete. Concentration afforded a residue which was suspended in water and the pH adjusted to 11 with K_2CO_3. The solid which formed was filtered and purified by radial chromatography [(2 mm plate), gradient elution 25% to 75% i-PrOH/CH_2Cl_2/1/10% NH_4OH] to afford a residue which was converted to the hydrochloride salt by dissolving the residue in i-PrOH and passing HCl gas over the solution. The solid was filtered, washed with i-PrOH and dried in a vacuum desicator to yield 169 mg (47%) of the title compound.

Elements	Calc	Found	
Carbon	51.61	51.83	$C_{15}H_{18}N_4O$ *2.15 HCl *0.1 H_2O*0.15iPr0H
Hydrogen	6.04	6.06	
Nitrogen	15.58	15.44	MW 359.54
Chlorine	21.20	21.11	

Example 18

(S-N-(1-Azabicyclo[2.2.2]octan-3-yl)imidazo[1,2-a]pyridine-2-carboxamide dihydrochloride)



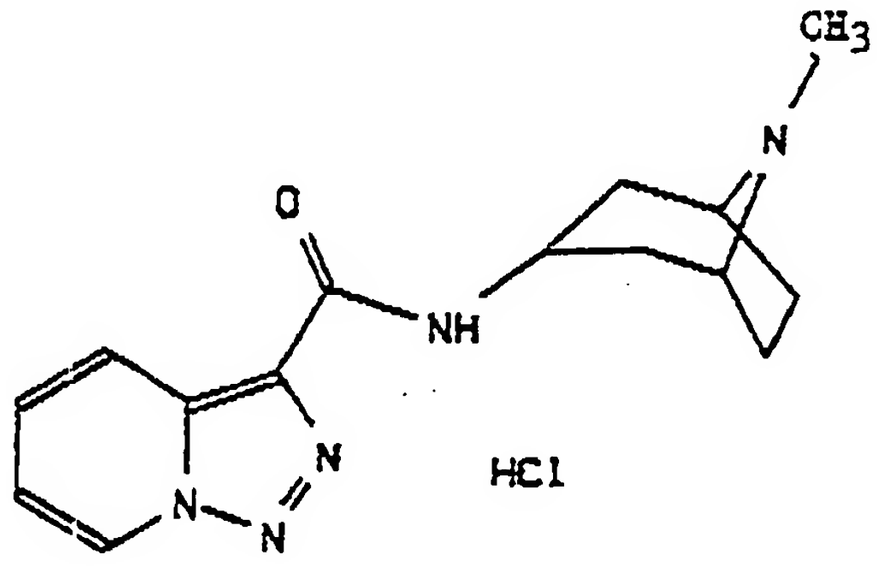
Procedure

Employing the compound of example E (216 mg, 0.001 mol), 1,1'-carbonyldiimidazole (178 mg, 0.001 mol) DMF (5 ml), S-3-aminoquinuclidine dihydrochloride (200 mg, 0.001 mol) [synthesized using the procedure in European Patent #0 280 603], the same procedure described in example 17 was used to afford the title compound (182 mg, 50%).

Elements	Calc	Found	
Carbon	51.18	51.53	$C_{15}H_{18}N_4O$ *2.1 HCl *0.4 H_2O*0.2 i-PrOH
Hydrogen	6.19	6.02	
Nitrogen	15.30	15.19	MW 366.13
Chlorine	20.33	20.09	

Example 19

Endo-N-(8-Methyl-8-azabicyclo[3.2.1]octane-3-yl) triazolylpyridine-3-carboxamide)monohydrochloride



Triazolylpyridine-3-carboxylic acid (110 mg, .606 mmole)[prepared In accordance with the procedure in

Chem. Ber., 1968, 99, 2918], was suspended in CH_2Cl_2 (5 ml). Thionyl chloride (442 µl, 6.60 mmole) and DMF (1 drop) were added and the mixture heated to reflux for 2.5 hr. Solvent was removed via rotary evaporator to give a solid. The solid was dissolved in CH_2Cl_2 (5 ml), and a solution of endo-N-8-methyl-8-azabicyclo[3.2.1) octane-3-amine (85.0 mg, .606 mmole), triethyl amine (338 µl, 2.43 mmole) in CH_2Cl_2(1 ml) was added and the mixture stirred for 50 hours. Filtration afforded an organic solution which was chromatographed on silica gel eluting with 10% CH_3OH/1% NH_4OH/CH_2Cl_2 to give 145 mg (80%) of the title compound as the free base. The free base was converted to the hydrochloride salt by the method described in Example 15A to yield 51 mg (33%) as the HCl salt.

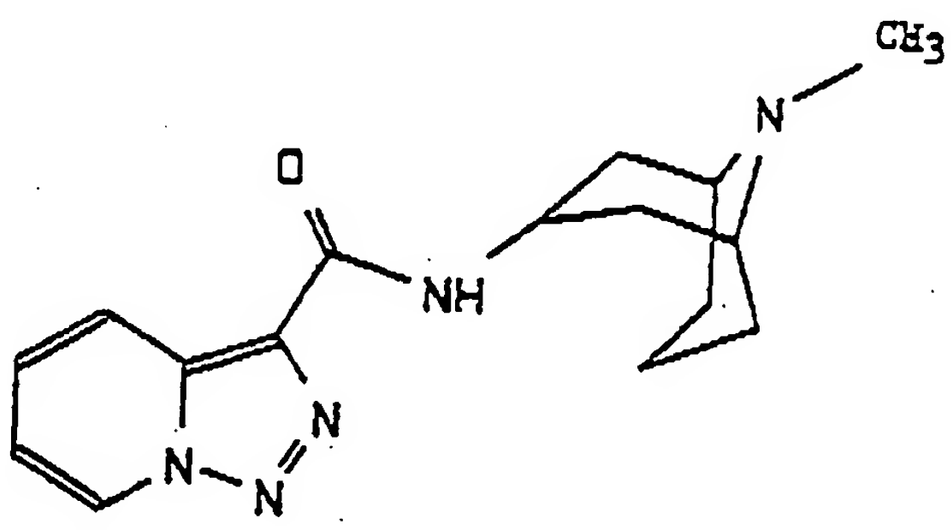
Anal: Calculated for $C_{15}H_{19}N_3O \cdot HCl. .2H_2O$
C, 55.37
H, 6.01
N, 21.52
Cl, 10.90

mp = 237-245°C

Found
55.08
6.26
21.97
11.08

Example 20

Endo-N-(9-Methyl-9-azabicyclo[3.3.1]nonan-3-yl) triazolylpyr-3-carboxamide)monohydrochloride



Triazolylpyridine-3-carboxlic acid (120.0 mg, .661 mmole) was suspended in CH_2Cl_2 (.5 ml). Thionyl chloride (481 µl, 6.61 mmole) and DMF (1 drop) were added and the mixture stirred for 2 1/2 hours. Concentration afforded a solid. The solid was dissolved in CH_2Cl_2, and a suspension of endo-N-9-methyl-9-azabicyclo[3.3.1]-nonane-3-amine (150 mg .661 mmole) and triethyl amine (369µl, 2.64 mmole) in CH_2Cl_2 - (2 ml) was added. The mixture was stirred 18 hours. The contents were washed with 5% K_2CO_3, water, and dried over $MgSO_4$. Filtration and concentration gave a foam. The residue was chromatographed on silica 60 eluting with 5% $CH_3OH(NH_3$†)/$CHCl_3$ to give 97 mg (49%) of a white foam as the free base. The free base was converted to the HCl salt by the method described in Example 15A to give 44 mg of the title compound (71%) as a solid.

Anal: Calculated $C_{16}H_{21}N_5O$ .9HCl 1.3H_2O	C, 54.04;	H, 6.94;
	N, 19.69;	Cl, 8.97;
Found:	C, 54.50;	H, 6.36;
	N, 19.05;	Cl, 9.31
m.p. = 225-233°C		

The compounds herein exhibit 5-HT3 antagonism. 5-HT3 antagonism can be determined by the radioligand receptor binding assay as described herein and in the in vivo Bezold-Jarisch reflex procedure.

Serotonin (5-HT_3)

Procedure:

GR65630 binds to the 5-HT_3 receptor. Brain cortices are obtained from male rats and a membrane fraction prepared by standard techniques. 0.04 mg of membrane prep is incubated with 0.2 nM [^{3}H]-GR656630 for 60 minutes at 22 ° C. Non-specific binding is estimated in the presence of 1 uM ICS 205-930. Membranes are filtered and washed 3 times and the filters are counted to determine [3H]-GR65630 specifically bound.*

Results:

Kd = 2.46 nM
Bmax = 154 fmol/mg protein
% Specific Binding: 70

Effect of Reference Compounds on [H]-GR65630 Bound (0.2 nM)			
Compound	IC_{50}	Ki	Hill Coefficient
Quipazine	0.5 nM	0.18 nM	0.86
ICS 205-930	2.2 nM	0.51 nM	1.0
5-HT	122 nM	0.39 uM	1.0
RU24969	320 nM	1.85 uM	1.0
Zacopride	0.55 nM	0.18 nM	0.86

Bezold-Jarisch Reflex

The test sample is administered i.p. (mg/kg) to a group of 3 mice. Thirty minutes later, a 5-HT (0.25 mg/kg i.v.)-induced bradycardia is recorded in pentobarbital anesthetized animals. A greater than 50 percent (>50) reduction in the bradycardic response relative to vehicle-treated control mice is considered significant.

REFERENCE AGENTS:	Minimum Effective Dose (MED), mg/kg
BRL-43694	0.05
cisapride	5
cyproheptadine	5
domperidone	>10
GR-38032	0.5
ketanserin	>10
mecamylamine	2.5
methysergide	>10
metoclopramide	5
scopolamine	2.5

This method has been described by Saxena, P. R. and Lawang, A., Arch. Int. Pharmacodyn., 277:235-252, 1985.

*Literature Reference:
Kilpatrick GJ, Jones BJ and Tyers MB. Identification and distribution of 5-HT_3 receptors in rat brain using radioligand binding. Nature, 330 : 746-748, 1987.

Example No.	TEST PROCEDURE	
	5-HT3 BINDING: NG108-15 Cells IC50	BEZOLD JARISCH REFLEX (Mice); % Inhibition @ Dose (IP)
1	6.3 nM 274 nM Ki = 137 nM	87% @ 10 73% @ 3 68% @ 1 N @ 0.3
2		53% @ 10 1% @ 5
3	19.34 nM 99 nM Ki = 50 nM	
4	500 nM 831 nM Ki = 416 nM	82% @ 10 2% @ 3
5	475 nM 628 nM Ki = 314 nM	80% @ 10 N @ 3
6	2.36 nM 9.8 nM Ki = 4.9 nM	
7	17.5 nM 23 nM Ki = 12 nM	
8	70 nM	100% @ 10 95% @ 5 88% @ 2.5 82% @ 0.5 N @ 0.25
9	16 nM 127 nM Ki = 64 nM	
10	200 nM 243 nM Ki = 122 nM	81% @ 10 N @ 3
11	> 100 nM	
12	17 nM	N @ 10
13	23% @ 100 nM	23% @ 10
14		N @ 10

Example No.	TEST PROCEDURE	
	5-HT3 BINDING: NG108-15 Cells IC50	BEZOLD JARISCH REFLEX (Mice); % Inhibition @ Dose (IP)
15	26.33 nM	
16	30 nM	

Also embraced within this invention is a class of pharmaceutical compositions comprising one or more of the described compounds in association with one or more non-toxic, pharmaceutically acceptable carriers and/or diluents and/or adjuvants (collectively referred to herein as "carrier" materials) and, if desired, other active ingredients. The compounds of the present invention may be administered by any suitable route, preferably in the form of a pharmaceutical composition adapted to such a route, and in a dose effective for the treatment intended. Therapeutically effective doses of the compounds of the present invention required to prevent or arrest the progress of the medical condition are readily ascertained by one of ordinary skill in the art. The compounds and composition may, for example, be administered intravascularly, intraperitoneally, subcutaneously, intramuscularly or topically.

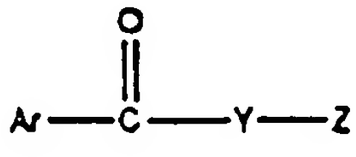
For oral administration, the pharmaceutical composition may be in the form of, for example, a tablet, capsule, suspension or liquid. The pharmaceutical composition is preferably made in the form of a dosage unit containing a particular amount of the active ingredient. Examples of such dosage units are tablets or capsules. These may with advantage contain an amount of active ingredient from about 1 to 250 mg, preferably from about 25 to 150 mg. A suitable daily dose for a mammal may vary widely depending on the condition of the patient and other factors. However, a dose of from about 0.1 to 3000 mg/kg body weight, particularly from about 1 to 100 mg/kg body weight, may be appropriate.

For therapeutic purposes, the compounds of this invention are ordinarily combined with one or more adjuvants appropriate to the indicated route of administration. If administered per os, the compounds may be admixed with lactose, sucrose, starch powder, cellulose esters of alkanoic acids, cellulose alkyl esters, talc, stearic acid, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulfuric acids, gelatin, acacia gum, sodium alginate, polyvinylpyrrolidone, and/or polyvinyl alcohol, and then tableted or encapsulated for convenient administration. Such capsules or tablets may contain a controlled-release formulation as may be provided in a dispersion of active compound in hydroxypropylmethyl cellulose. Formulations for parenteral administration may be in the form of aqueous or non-aqueous isotonic sterile injection solutions or suspensions. These solutions and suspensions may be prepared from sterile powders or granules having one or more of the carriers or diluents mentioned for use in the formulations for oral administration. The compounds may be dissolved in water, polyethylene glycol, propylene glycol, ethanol, corn oil, cottonseed oil, peanut oil, sesame oil, benzyl alcohol, sodium chloride, and/or various buffers. Other adjuvants and modes of administration are well and widely known in the pharmaceutical art.

Although this invention has been described with respect to specific embodiments, the details of these embodiments are not to be construed as limitations. Various equivalents, changes and modifications may be made without departing from the spirit and scope of this invention, and it is understood that such equivalent embodiments are part of this invention.

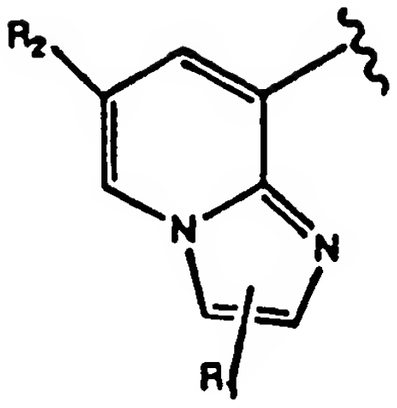
Claims

1. A compound of the formula

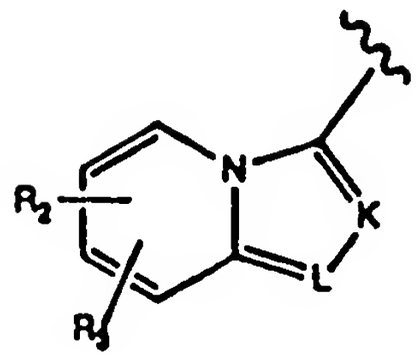


the stereoisomers and pharmaceutically acceptable salts thereof, wherein Ar represents a radical of the

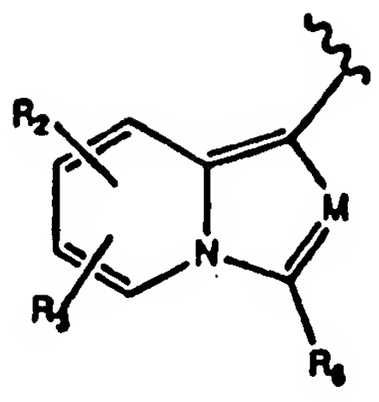
formula



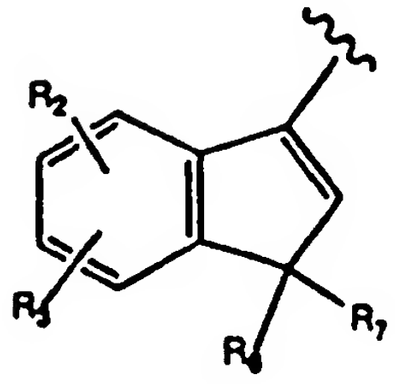
A



B



C



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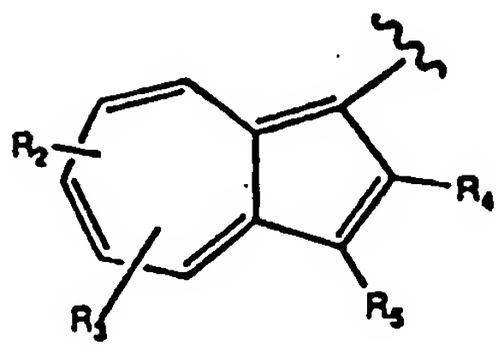
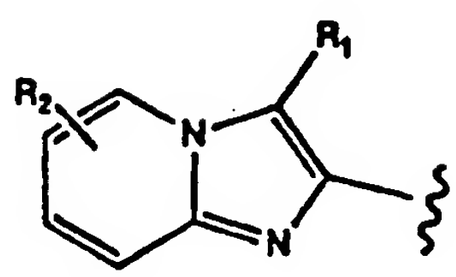


E



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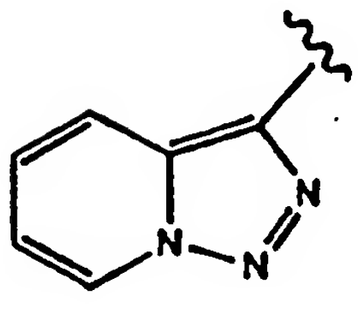
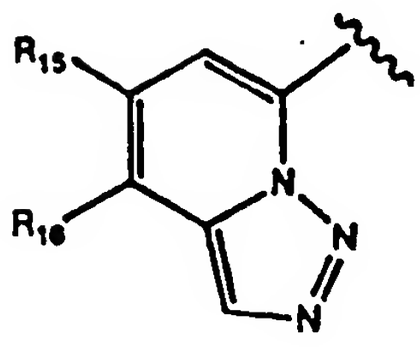


G



H

Wherein in group A R_1 is H, or C_{1-6} alkyl, and R_2 is H, or halogen;

In group B, K is N or CR_4, L is N or CR_5, R_2 & R_3 are independently H or halogen, R_4 is H, or C_{1-6} alkoxy and R_5 is H, halogen, CF_3, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkythio, C_{1-6} alkylsulfonyl, C_{1-6} alkylsulfinyl, C_{1-7} acyl, cyano, C_{1-6} alkoxycarbonyl, C_{1-7} acylamino, hydroxy, nitro, amino, aminocarbonyl, or aminosulfonyl optionally N-substituted by one or two groups selected from C_{1-6} alkyl, C_{3-8} cycloalkyl, and C_{3-8} cycloalkylC_{1-4}alkyl or disubstituted by C_4 or C_5 polymethylene; phenyl or phenyl C_{1-4} alkyl group optionally substituted in the phenyl ring by one or two of halogen, C_{1-6} alkoxy or C_{1-6} alkyl groups;

In group C, M is N or CR_4, R_2 & R_3 are independently H or halogen, R_4 is H or C_{1-6} alkoxy and R_5 is H, halogen, CF_3, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkylsulfonyl, C_{1-6} alkylsulfinyl, C_{1-7} acyl, cyano, C_{1-6} alkoxycarbonyl, C_{1-7} acylamino, hydroxy, nitro, amino, aminocarbonyl, or aminosulfonyl optionally N-substituted by one or two groups selected from C_{1-6} alkyl, C_{3-8} cycloalkyl, and C_{3-8} cycloalkylC_{1-4}alkyl or disubstituted by C_4 or C_5 polymethylene, phenyl or phenyl C_{1-4} alkyl group optionally substituted in the phenyl ring by one or two of halogen, C_{1-6} alkoxy or C_{1-6} alkyl groups;

In group D one of R_6 and R_7 is C1-6 alkyl and the other is C_{1-6} alkyl, phenyl or phenyl C_{1-4} alkyl optionally substituted in either phenyl ring by one or two of C_{1-6} alkyl, C_{1-6} alkoxy, or halogen, or R_6 & R_7 together are C_{2-6} polymethylene or C_{2-5} polymethylene intertupted by an -O-linkage, and R_2 & R_3 are independently H or halogen;

In group E, R_4 is H or C_{1-6} alkoxy, R_5 is H or C_{1-6} alkoxy, and R_2 is H, halogen, CF_3, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkylsulfonyl, C_{1-6} alkylsulfinyl, C_{1-7} acyl, cyano, C_{1-6} alkoxycarbonyl, C_{1-7} acylamino, hydroxy, nitro, amino, aminocarbonyl, or aminosulfonyl, optionally N-substituted by one or two groups selected from C_{1-6} alkyl, C_{3-8} cycloalkyl, and C_{3-8} cycloalkylC_{1-4}alkyl or disubstituted by C_4 or C_5 polymethylene, phenyl or phenyl C_{1-4} alkyl group optionally substituted in the phenyl ring by one or two of halogen, C_{1-6} alkoxy or C_{1-6} aikyl groups, and R_2 & R_3 are independently H or halogen;

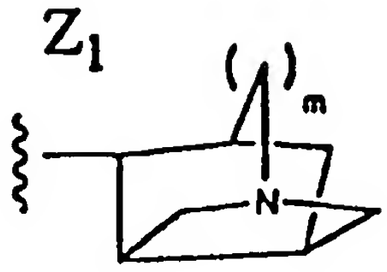
In group F, R_1 is H or C_{1-6} alkyl, and R_2 is H or halogen; and

In group H, R_{15} & R_{16} are independently H or -CH=CH-CH=CH-;

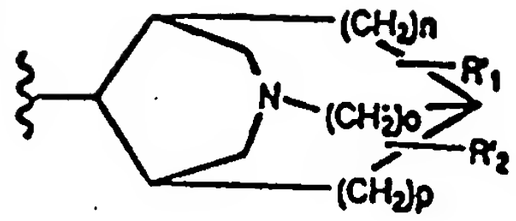
Y represents NH or O; and

Z represents a radical of the formula

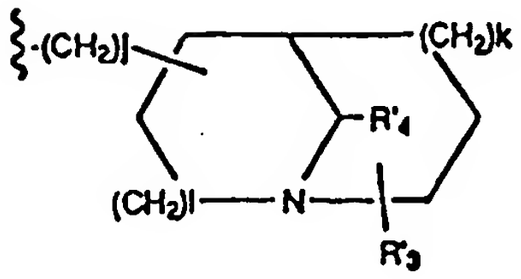
Z_1



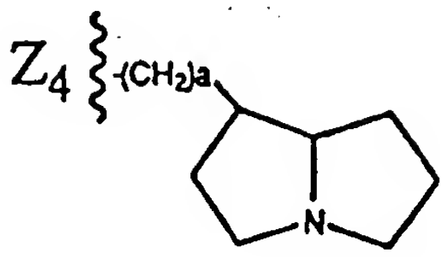
Z_2



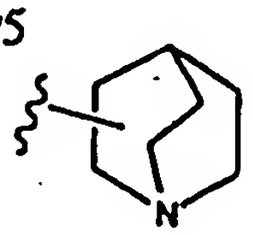
Z_3



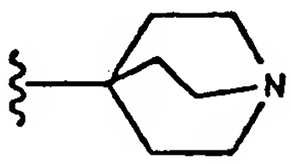
Z_4



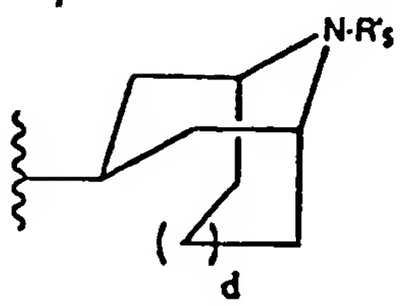
Z_5



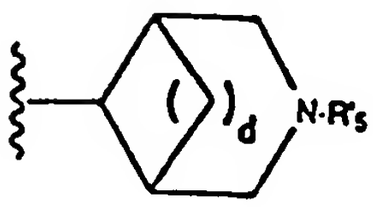
Z_6



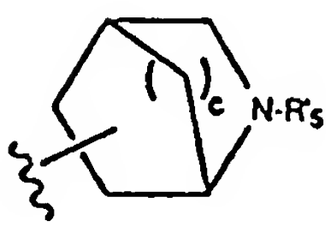
Z_7



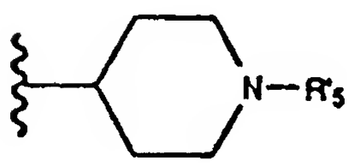
Z_8



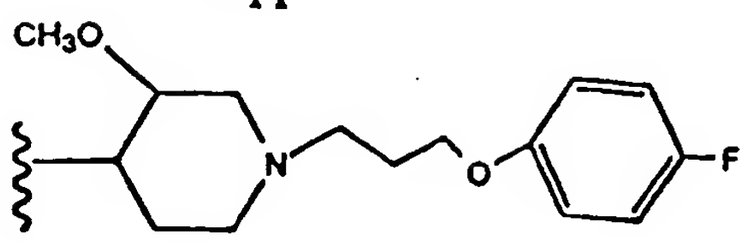
Z_9



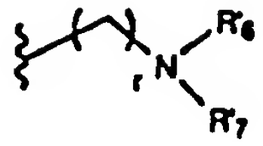
Z_{10}



Z_{11}



Z_{12}



Wherein in group Z_1 m is 1 or 2;

In group Z_2 n and p are independently 1 or 2 and o is 0, 1, or 2 such that $n + p + o \geq 3$, and R'_1 and R'_2 are independently H, C_{1-6} alkyl, phenyl or phenyl-C_{1-6} alkyl, which phenyl moieties may be substituted by C_{1-6} alkyl, C_{1-6} alkoxy, or halogen;

In group Z_3 k is 0 to 2, l is 0 to 3, j is 0 to 4, and one of R'_3 and R'_4 is H, C_{1-6} alkyl, phenyl, or phenyl-C_{1-3} alkyl, which phenyl moieties may be optionally substituted by C_{1-6} alkyl, C_{1-6} alkoxy, CF_3 or halogen, and the other of R'_3 and R'_4 is H or C_{1-6} alkyl;

In group Z_4 a is 0 or 1;

In group Z_7 d is 0 or 1, and R'_5 is C_{1-7} alkyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkyl-C_{1-2} alkyl, C_{2-7} alkenyl, C_{2-7} alkylenyl-C_{1-4} alkyl, or phenyl-C_{1-6} alkyl.

In group Z_8 d and R'_5 are as previously defined;

In group Z_9 e is 1 or 2, and R'_5 is as previously defined;

In group Z_{10} R'_5 is as previously defined; and

In group Z_{12} r is 1 to 4, R'_6 and R'_7 are independently C_{1-6} alkyl, C_{1-6} alkenyl, or C_{1-6} alkynyl or together form -(CH_2)s-, wherein s is 3-7 and one of the CH_2 units may optionally be replaced by -0-, or NR'_8, wherein R'_8 is H or C_{1-6} alkyl;

with the proviso that when Ar is group B, C, D or E, then Z cannot be Z_5, Z_7 or Z_9.

2. A compound of Claim 1 wherein Z is selected from the group consisting of Z_1, Z_3, Z_5 and Z_7.

3. A compound of Claim 1 wherein Ar is group A wherein R_1 is H and R_2 is H or halo,
Y is NH, and
Z is selected from the group consisting of
Z_1 wherein m is 1;
Z_2 wherein n, o and p are 1
and R'_1 and R'_2 are both H;
Z_3 wherein k and l are both 1,
j is 0 and $R_{3'}$ and R_4' are both H;
Z_5;
Z_7 wherein d is 0 or 1 and R'_5 is C_{1-7} alkyl;
Z_{10} wherein R'_5 is phenylalkyl;
Z_{11}; and
Z_{12} wherein r is 1 and R'_6 and R'_7 are both C_{1-6} alkyl.

4. A compound of Claim 3 wherein in group A R_2 is chloro, and Z is Z_5 or Z_7.

5. The compound of Claim 1 which is (endo-N-(1-Azabicyclo[3.3.1]nonan-4-yl)-6-chloroimidazo[1,2-a]-pyridine-8-carboxamide, dihydrochloride).

6. The compound of Claim 1 which is (endo-N-(1-Azabicyclo[3.3.1]nonan-4-yl)imidazo[1,2-a]pyridine-8-carboxamide, dihydrochloride).

7. The compound of Claim 1 which is (endo-N-(8-Methyl-8-azabicyclo[3.2.1]octan-3-yl)-6-chloroimidazo-[1,2-a]pyridine-8-carboxamide, dihydrochloride).

8. The compound of Claim 1 which is (endo-N-(8-methyl-8-azabicyclo[3.2.1]octan-3-yl)imidazo[1,2-a]-pyridine-8-carboxamide, hydrochloride).

9. The compound of Claim 1 which is (exo-N-(8-methyl-8-azabicyclo[3.2.1]octan-3-yl)imidazo[1,2-a]-pyridine-8-carboxamide, hydrochloride).

10. The compound of Claim 1 which is (endo-N-(9-Methyl-9-azabicyclo[3.3.1]nonan-3-yl)-6-chloroimidazo-[1,2-a]pyridine-8-carboxamide hydrochloride).

11. The compound of Claim 1 which is (N-(1-Azabicyclo[2.2.2]octan-3-yl)-6-chloroimidazo[1,2-a]pyridine-8-carboxamide dihydrochloride).

12. The compound of Claim 1 which is (N-(1-Azabicyclo[2.2.2]octan-3-yl)imidazo[1,2-a]pyridine-8-carbox-amide, dihydrochloride).

13. The compound of Claim 1 which is ((±)-endo-N-(Hexahydro-1H-2-,5β-methano-3aα,6aα-cyclopenta[c]-

pyrrol-4α-yl)-6-chloroimidazo[1,2-a]pyridine-8-carboxamide, monohydrochloride).

14. The compound of Claim 1 which is ((±)-endo-N-(Hexahydro-1H-2,5β-methano-3aα,6aα-cyclopenta[c]-pyrrol-4α-yl)imidazo[1,2-a]pyridine-8-carboxamide, hydrochloride).

15. The compound of Claim 1 which is (exo-N-(1 azatricyclo[3.3.1.$1^{3,7}$]decan-4-yl)-6-chloroimidazo[1,2-a]-pyridine-8-carboxamide, monohydrochloride).

16. The compound of Claim 1 which is (N-[2-(Diethylamino)ethyl]imidazo[1,2-a]pyridine-8-carboxamide).

17. The compound of Claim 1 which is (Cis-N-[[3-(4-Fluorophenoxy)propyl]-3-methoxy-4-piperidinylamine]-imidazo[1,2-a]pyridine-8-carboxamide).

18. The compound of Claim 1 which is ((±)-endo-N-(Hexahydro-1H-2,5β-methano-3aα,6aα-cyclopenta[c]-pyrrol-4aα-yl)-3-ethylindolizine-1-carboxamide monohydrochloride).

19. The compound of Claim 1 which is ((±)-endo-N-(Hexahydro-1H,2,5β-methano-3aα,6aα-cyclopenta[c]-pyrrol-4α-yl)-3-ethylimidazo[1,5-a]pyridine-1-carboxamide, monohydrochloride).

20. The compound of Claim 1 which is (R-N-(1-Azabicyclo[2.2.2]octan-3-yl)imidazo[1,2-a]pyridine-2-carbox-amide dihydrochloride).

21. The compound of Claim 1 which is (S-N-(1-Azabicyclo[2.2.2]octan-3-yl)imidazo[1,2-a]pyridine-2-carbox-amide dihydrochloride).

22. A pharmaceutical composition for the treatment of anxiety, psychoses, depression, substance abuse, cognitive disorders, gastrointestinal motility disturbancies or conditions responsive to 5-HT_3 antagonist effect comprising a therapeutically effective amount of a compound of Claim 1 and a pharmaceutically acceptable carrier or diluent.

23. A pharmaceutical composition of Claim 22 wherein Z is selected from the group consisting of Z_1, Z_3, Z_5 and Z_7.

24. A pharmaceutical composition of claim 22 wherein Ar is group A wherein R_1 is H and R_2 is H or halo,
Y is NH, and
Z is selected from the group consisting of
Z_1 wherein m is 1;
Z_2 wherein n, o and p are each 1
and R'_1 and R'_2 are both H;
Z_3 wherein k and l are both 1, j is 0 and
R'_3 and R'_4 are both H;
Z_5;
Z_7 wherein d is 0 or 1 and R'_5 is C_{1-7} alkyl;
Z_{10} wherein R'_5 is phenylalkyl
Z_{11}; and
Z_{12} wherein r is 1 and R'_6 and R'_7 are both C_{1-6} alkyl.

25. A pharmaceutical composition of Claim 24 wherein in group A R_2 is chloro, and Z is Z_5.

26. A pharmaceutical composition of Claim 24 wherein Z is Z_7 wherein d is 0 or 1 and R'_5 is C_{1-7} alkyl.

27. The pharmaceutical composition of Claim 22 wherein the compound is (endo-N-(1-Azabicyclo[3.3.1]-nonan-4-yl)-6-chloroimidazo[1,2-a]pyridine-8-carboxamide, dihydrochloride).

28. The pharmaceutical composition of Claim 22 wherein the compound is (endo-N-(1-Azabicyclo[3.3.1]-nonan-4-yl)imidazo[1,2-a]pyridine-8-carboxamide, dihydrochloride).

29. The pharmaceutical composition of Claim 22 wherein the compound is (endo-N-(8-Methyl-8-azabicyclo-

[3.2.1]octan-3-yl)-6-chloroimidazo[1,2-a]pyridine-8-carboxamide, dihydrochloride).

30. The pharmaceutical composition of Claim 22 wherein the compound is (endo-N-(8-methyl-8-azabicyclo-[3.2.1]octan-3-yl)imidazo[1,2-a]pyridine-8-carboxamide, hydrochloride).

31. The pharmaceutical composition of Claim 22 wherein the compound is (exo-N-(8-methyl-8-azabicyclo-[3.2.1]octan-3-yl)imidazo[1,2-a]pyridine-8-carboxamide, hydrochloride).

32. The pharmaceutical composition of Claim 22 wherein the compound is (endo-N-(9-Methyl-9-azabicyclo-[3.3.1]nonan-3-yl)-6-chloroimidazo[1,2-a]pyridine-8-carboxamide hydrochloride).

33. The pharmaceutical composition of Claim 22 wherein the compound is (N-(1-Azabicyclo[2.2.2]octan-3-yl)-6-chloroimidazo[1,2-a]pyridine-8-carboxamide dihydrochloride).

34. The pharmaceutical composition of Claim 22 wherein the compound is (N-(1-Azabicyclo[2.2.2]octan-3-yl)imidazo[1,2-a]pyridine-8-carboxamide, dihydrochloride).

35. The pharmaceutical composition of Claim 22 wherein the compound is ((±)-endo-N-(Hexahydro-1H-2-,5β-methano-3aα,6aα-cyclopenta[c]pyrrol-4α-yl)-6-chloroimidazo[1,2-a]pyridine-8-carboxamide, monohydrochloride).

36. The pharmaceutical composition of Claim 22 wherein the compound is ((±)-endo-N-(Hexahydro-1H-2,5β-methano-3aα,6aα-cyclopenta[c]pyrrol-4α-yl)imidazo[1,2-a]pyridine-8-carboxamide, hydrochloride).

37. The pharmaceutical composition of Claim 22 wherein the compound is (exo-N-(1-azatricyclo[3.3.1.$1^{3,7}$]-decan-4-yl)-6-chloroimidazo[1,2-a]pyridine-8-carboxamide, monohydrochloride).

38. The pharmaceutical composition of Claim 22 wherein the compound is (N-[2-(Diethylamino)ethyl]-imidazo[1,2-a]pyridine-8-carboxamide).

39. The pharmaceutical composition of Claim 22 wherein the compound is (Cis-N-[[3-(4-Fluorophenoxy)-propyl]-3-methoxy-4-piperidinylamine]imidazo[1,2-a]pyridine-8-carboxamide).

40. The pharmaceutical composition of Claim 22 wherein the compound is ((±)-endo-N-(Hexahydro-1H-2,5β-methano-3aα,6aα-cyclopenta[c]pyrrol-4aα-yl)-3-ethylindolizine-1-carboxamide monohydrochloride).

41. The pharmaceutical composition of Claim 22 wherein the compound is ((±)-endo-N-(Hexahydro-1H,2,5β-methano-3aα,6aα-cyclopenta[c]pyrrol-4α-yl)-3-ethylimidazo[1,5-a]pyridine-1-carboxamide, monohydrochloride).

42. The pharmaceutical composition of Claim 22 wherein the compound is (R-N-(1-Azabicyclo[2.2.2]octan-3-yl)imidazo[1,2-a]pyridine-2-carboxamide dihydrochloride).

43. The pharmaceutical composition of Claim 22 wherein the compound is (S-N-(1-Azabicyclo[2.2.2]octan-3-yl)imidazo[1,2-a]pyridine-2-carboxamide dihydrochloride).

44. Use of a compound of Claim 1 for preparing a medicament for treating anxiety, psychoses, depression or gastrointestinal motility disturbancies.

45. Use according to Claim 44 wherein Z of the compound is selected from the group consisting of Z_1, Z_3, Z_5 and Z_7.

46. Use according to Claim 44 wherein Ar of the compound is group A wherein R_1 is H and R_2 is H or halo,
Y is NH, and
Z is selected from the group consisting of
Z_1 wherein m is 1;
Z_2 wherein n, o and p are each 1

and R'_1 and R'_2 are both H;
Z_3 wherein k and l are both 1,
j is 0 and R_3' and R_4' are both H;
Z_5;
Z_7 wherein d is 0 or 1 and R'_5 is C_{1-7} alkyl;
Z_{10} wherein R'_5 is phenylalkyl;
Z_{11}; and
Z_{12} wherein r is 1 and R'_6 and R'_7 are both C_{1-6} alkyl.

47. Use according to Claim 46 wherein in group A R_2 is cloro, and Z is Z_5 or Z_7.

48. Use according to Claim 44 wherein the compound is (endo-N-(1-Azabicyclo[3.3.1]nonan-4-yl)-6-chloroimidazo[1,2-a]pyridine-8-carboxamide, dihydrochloride).

49. Use according to Claim 44 wherein the compound is (endo-N-(1-Azabicyclo[3.3.1]nonan-4-yl)imidazo-[1,2-a]pyridine-8-carboxamide, dihydrochloride).

50. Use according to Claim 44 wherein the compound is (endo-N-(8-Methyl-8-azabicyclo[3.2.1]octan-3-yl)-6-chloroimidazo[1,2-a]pyridine-8-carboxamide, dihydrochloride).

51. Use according to Claim 44 wherein the compound is (endo-N-(8-methyl-8-azabicyclo[3.2.1]octan-3-yl)-imidazo[1,2-a]pyridine-8-carboxamide, hydrochloride).

52. Use according to Claim 44 wherein the compound is (exo-N-(8-methyl-8-azabicyclo[3.2.1]octan-3-yl)-imidazo[1,2-a]pyridine-8-carboxamide, hydrochloride).

53. Use according to Claim 44 wherein the compound is (endo-N-(9-Methyl-9-azabicyclo[3.3.1]nonan-3-yl)-6-chloroimidazo[1,2-a]pyridine-8-carboxamide hydrochloride).

54. Use according to Claim 44 wherein the compound is (N-(1-Azabicyclo[2.2.2]octan-3-yl)-6-chloroimidazo-[1,2-a]pyridine-8-carboxamide dihydrochloride).

55. Use according to Claim 44 wherein the compound is (N-(1-Azabicyclo[2.2.2]octan-3-yl)imidazo[1,2-a]-pyridine-8-carboxamide, dihydrochloride).

56. Use according to Claim 44 wherein the compound is ((±)-endo-N-(Hexahydro-1H-2-,5β-methano-3aα,6aα-cyclopenta[c]pyrrol-4α-yl)-6-chloroimidazo[1,2-a]pyridine-8-carboxamide, monohydrochloride).

57. Use according to Claim 44 wherein the compound is ((±)-endo-N-(Hexahydro-1H-2,5β-methano-3 aα,6aα-cyclopenta[c]pyrrol-4α-yl)imidazo[1,2-a]pyridine-8-carboxamide, hydrochloride).

58. Use according to Claim 44 wherein the compound is (exo-N-(1-azatricyclo[3.3.1.$1^{3,7}$]decan-4-yl)-6-chloroimidazo[1,2-a]pyridine-8-carboxamide, monohydrochloride).

59. Use according to Claim 44 wherein the compound is (N-[2-(Diethylamino)ethyl]imidazo[1,2-a]pyridine-8-carboxamide).

60. Use according to Claim 44 wherein the compound is (Cis-N-[[3-(4-Fluorophenoxy)propyl]-3-methoxy-4-piperidinylamine]imidazo[1,2-a]pyridine-8-carboxamide).

61. Use according to Claim 44 wherein the compound is ((±)-endo-N-(Hexahydro-1H-2,5β-methano-3 aα,6aα-cyclopenta[c]pyrrol-4aα-yl)-3-ethylindolizine-1-carboxamide monohydrochloride).

62. Use according to Claim 44 wherein the compound is ((±)-endo-N-(Hexahydro-1H,2,5β-methano-3 aα,6aα-cyclopenta[c]pyrrol-4α-yl)-3-ethylimidazo[1,5-a]pyridine-l-carboxamide,monohydrochloride).

63. Use according to Claim 44 wherein the compound is (R-N-(1-Azabicyclo[2.2.2]octan-3-yl)imidazo[1,2-a]-pyridine-2-carboxamide dihydrochloride).

64. Use according to Claim 44 wherein the compound is (S-N-(1-Azabicyclo[2.2.2]octan-3-yl)imidazo[1,2-a]-pyridine-2-carboxamide dihydrochloride).

65. Use of a compound of Claim 1 for preparing a medicament for treating a condition responsive to 5-HT_3 antagonism.

66. Use according to Claim 65 wherein Z is selected from the group consisting of Z_1, Z_3, Z_5 and Z_7.

67. Use according to Claim 66 wherein Ar is group A wherein R_1 is H and R_2 is H or halo,
Y is NH, and
Z is selected from the group consisting of
Z_1 wherein m is 1;
Z_2 wherein n, o and p are each 1
and R'_1 and R'_2 are both H;
Z_3 wherein k and l are both 1,
j is 0 and R_3' and R_4' are both H;
Z_5;
Z_7 wherein d is 0 or 1 and R'_5 is C_{1-7} alkyl;
Z_{10} wherein R'_5 is phenylalkyl;
Z_{11}; and
Z_{12} wherein r is 1 and R'_6 and R'_7 are both C_{1-6} alkyl.

68. Use according to Claim 67 wherein in group A R_2 is chloro, and Z is Z_5 or Z_7.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 92 10 3862

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
X	EP-A-0 254 584 (BEECHAM) * complete document * ---	1,22	C07D519/00 C07D471/04 A61K31/435 //(C07D519/00, 471:00,471:00) (C07D519:00, 471:00,451:00) (C07D519:00, 471:00,453:00) (C07D519:00, 487:00,471:00) (C07D471:00, 235:00,221:00)
X	EP-A-0 289 170 (BEECHAM) * complete document * -----	1,22	

TECHNICAL FIELDS SEARCHED (Int. Cl.5)

C07D
A61K

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	09 JULY 1992	ALFARO FAUS I.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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